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Predictive Genetic Tests and Health Care Costs: Final Report Prepared for the Ontario Ministry of Health and Long Term Care

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Executive Summary

Genetic testing has long been part of Canada's health system, but the scope of genetic testing is growing into new areas. Whereas traditional tests predominantly foretell the health of future generations, new tests increasingly tell individuals about their own health and risks. And whereas traditional tests have focused on rare, single-gene, genetically determined disorders, new tests target common, complex, and multifactorial diseases in which genetics plays only a part. These trends lead to unprecedented clinical and popular interest in genetic tests, and the expanded use of testing will affect both population health and health care costs. Whether the net effects will be positive or negative is a matter of heated debate. Early policy decisions about how tests will be disseminated, provided, and funded will greatly influence the cost and other impacts of new predictive genetic tests.

This report examines the potential effect of new predictive genetic test services on health care costs. We offer a general framework that identifies key factors determining the cost impact of a predictive genetic test service and suggests how the choices of health system decision makers influence costs. We also present cost analyses of four specific predictive genetic tests. The report focuses solely on financial cost implications from the formal health care system's point of view, and does not address the very important questions of impacts on health, wellbeing, productivity, societal costs, or informal care giving

The cost impact of a predictive genetic test depends on, among other things, characteristics of the test, the scope of its application, and the changes in health care utilization (disease surveillance, prevention, and treatment) induced by the test result. For many tests, the cost of performing the test itself makes up only a small proportion of the total health care costs that follow from its use.

Predictive genetic tests cannot be meaningfully analyzed as one monolithic health technology. We distinguish three types of predictive genetic tests on the basis of their predictive power and the genetic nature of the health conditions they address. Full Penetrance tests are used to predict diseases in which a genetic mutation causes the disease in all individuals with the

condition. That is, those with the mutation will get the disease, and virtually all those with the disease have the mutation. Such tests are highly predictive and such conditions are rare (e.g., Huntington's disease). Predisposition tests are highly, but not fully, predictive for relatively rare conditions with a strong genetic component (e.g., familial breast cancer). A substantial proportion of individuals with the genetic mutation will develop the condition while those without the marker will not. Risk factor tests have much lower predictive power, and are used to predict common, multifactorial conditions in which genetics plays a limited role (e.g., heart disease). While individuals with the genetic mutation are at increased risk for the health condition, most will not succumb to it, while many without the genetic mutation will.

The effective predictive power of a genetic test depends upon both the diagnostic features of the test itself (how well can it distinguish those with and without the genetic mutation), the relation between the genetic mutation and the likelihood of developing the disease, and the epidemiology of the population in which it is applied, including the underlying prevalence of the genetic mutation and the disease of concern. Even an excellent, highly predictive test will generate a very high proportion of false results (e.g., the majority of "positives" being false) if applied to a low risk population. Full penetrance and predisposition tests are of least concern in this respect as they have natural target populations: individuals identified by the clinical hallmarks of the condition or by biological relationship to an individual already identified as having the condition. Risk factor tests, in contrast, may apply to the general population for screening purposes, and therefore are more susceptible to generating false and clinically misleading results. The actual target populations for a genetic test will depend on such issues as system capacity, patient and clinician demand, options for clinical management (i.e., surveillance, prevention and treatment), and gatekeeping structures (e.g., referral protocols, designated providers, direct consumer marketing).

The effect of the genetic testing service on health care costs depends on the pattern by which the test classifies tested individuals as "positive" (has genetic mutation) and negative (does not have genetic mutation), and how individuals with each of these results changes their health care consumption patterns. To estimate the cost impact of a test, therefore, one must model what individuals do based on the new genetic information they get from the test, as well as

what they would have done without it. Four basic categories of health care expenditure that might change include: (1) cost of identifying those who will develop the disease; (2) the cost of surveillance among those thought to be at high risk; (3) the cost of preventive care; and (4) the cost of treatment if the disease occurs. The effects on each of these types of costs depends not only on the test itself, but also on individual and provider behaviour, the current state-of-the-art of clinical practice with respect to non-genetic screening, surveillance, prevention, and treatment technologies. New developments in any of these three areas will affect clinical options, behavioural choices, and their consequent costs. If a genetic test replaces the use of a more expensive non-genetic test, then the genetic test could reduce the overall costs of case-finding; if, however, it is use in addition to existing case-finding services, it will be cost increasing. Similarly, if the current practice is to conduct disease surveillance on high risk individuals and/or for such individuals to utilize preventive services, if the test allows us to definitively determine that a person is not at risk, it could again reduce health care costs. In contrast, if a test, especially one that results in a large number of false positives, induces large number of people to unnecessarily utilize surveillance or preventive services, then the test will be cost increasing. Finally, predictive genetic tests could reduce treatment costs if it encourages truly high risk individuals to utilize effective surveillance or preventive services that reduce the occurrence or severity of disease.

Full penetrance tests will, on average, have the smallest impact on aggregate costs because the diseases with which they are associated are rare and because they are easiest to target on high-risk individuals. Risk factor tests likely have the largest variance in their impact on aggregate costs because they have the potential to affect large sections of the population.

We present cost analyses for four specific predictive genetic tests: Familial Adenomatous Polyposis (FAP), Herditary Nonpolyposis Colorectal Cancer (HNPCC), Hereditary Hemochromatosis (HH), and APOE testing for alzheimer's disease. FAP is a full penetrance test, HNPCC and HH are predisposition tests, and APOE is a risk factor test. The cost analyses for HNPCC and HH are based only on the published literature; the cost analyses for FAP and APOE combine evidence from the published literature and an original costing exercise. The analysis indicates that on net, the test for FAP would reduce costs (the savings from reduced

surveillance costs exceed the cost of the test) by $1369 per person tested when testing is restricted to family members of individuals diagnosed with the disease. Because the disease is so rare, a test program would generate total savings of approximately $200,000 in Ontario. There is insufficient information to judge the cost impact of genetic testing for HNPCC. Based on figures from the literature, a targeted screening program for HH would generate savings of approximately $1 per person tested, leading to total savings of approximately $300,000 for Ontario. However, and untargeted screening program may generate increased costs up to $60 million. Finally, on balance, a program of APOE testing targeted at high-risk individuals already diagnosed with mild cognitive impairment, is estimated to increase health care costs by $579 per person tested. An estimate of the total cost impact, which is admittedly only a ballpark figure, is that the aggregate cost impact in Ontario for a program similar to the one analyzed would increase costs by $10 to $20 million. It must be emphasized that the above figures should not be interpreted as predictions of what would happen, but are meant only as rough estimates to indicate the order of magnitude of the cost impacts of the tests analyzed.

A range of considerations that cannot be included in the analyses of individual tests that will influence the ultimate impact of the development of predictive genetic tests on health care costs. We have little knowledge of how consumers and providers will respond to the information generated by the tests. Yet, their responses will be central to the ultimate cost impact. And their responses may well be influenced by the fact that, unlike non-genetic screening, for-profit corporations now hold exclusive patents on many genetic testing technologies. They have incentive to push for broad adoption of such tests and may pursue aggressive marketing practices to advance their economic interests. This may particularly be the case when organizations sell goods and services complementary to the genetic test (a practice already seen for non-genetic tests such as bone-densitometry and serum lipid testing).

Coverage decisions for predictive genetic tests will have to be made on a case-by-case basis. Three basic coverage options exist: (1) no public coverage with a private market allowed; (2) unrestricted public coverage; and (3) criteria-based public coverage. The first option opens the market for such tests to more market-oriented dynamics and, while it does save the public funder the cost of the test itself, it does not avoid the other health care costs, most of which will

be publicly financed. In the end, the costs savings would be small and the public funder has lesser ability to regulate use. The second case ensures broader access but will have the largest cost impact on the public funder. The third option, criteria-based public coverage, provides access to those in need while giving public funders the most levers to limit use to situations where the tests are most likely to produce benefits and avoid broad, inappropriate uptake that would generate large costs to the public system.

1.0 Introduction

Genetic testing has long been present in Canada's health system. Since the 1960s, most newborns in Canada have been tested for the presence of rare but treatable genetic metabolic diseases, such as phenylketonuria. Since the 1970s, pregnant women at high risk have been offered prenatal diagnosis for the detection of chromosomal conditions such as Down's Syndrome. But the shape and scope of genetic testing is changing. These changes are of two main kinds:

1. A change in focus from "future" generations to "ourselves". Genetic testing has traditionally assessed the risks of genetic disease in *future generations*. Such testing includes carrier screening, newborn screening and prenatal diagnosis. New forms of genetic testing, predictive genetic tests, provide information about health status and appropriate forms of treatment "*in ourselves*" (Welch and Burke 1998). That is predictive genetic tests provide information about the risk of onset of a genetic disorder or other disease in the tested individual. Used in asymptomatic individuals, they provide information regarding the individual's risk of developing a disease in the future.

   Much excitement surrounds these predictive genetic tests, though their ultimate health system impact is uncertain. Meanwhile, the older forms of genetic testing continue and may even expand together with the new predictive tests.

2. A change from rare, single-gene disorders to common, complex disorders. Early predictive genetic tests provided information about the future onset of rare, single-gene disorders. The candidate populations for such tests are small and thus, though these interventions may prove costly, the health system impacts of such tests are limited.

   Predictive genetic testing is expected to expand to include more common and complex disorders (Bell 1998; Collins 1999; Collins and McKusick 2001). Such tests will necessarily have a reduced predictive power. They also have the potential to be applied to larger populations and thus to have broader impacts on the health system.

High expectations accompany this new era of molecular medicine. Francis Collins, the head of the National Human Genome Research Institute of the US NIH, writes that,

> "Genetic prediction of individual risks of disease and responsiveness to drugs will reach the medical mainstream in the next decade or so. The development of designer drugs, based on a genomic approach to targeting molecular pathways that are disrupted in disease, will follow soon after" (Collins and McKusick 2001).

But so to does some skepticism. Other commentators insist that the population relevance of genetic testing will be too small to make a revolution: "We do not want to downplay the importance of highly penetrant susceptibility-conferring genotypes or inherited drug sensitivity," Neil Holtzman and Theresa Marteau write, "Nonetheless, neither category represents a large enough proportion of the population to warrant widespread screening. Testing in families with a history of the disease would be a more efficient approach but does not a revolution make"(Holtzman and Marteau 2000). Finally, some commentators caution that, whatever the final impact of new genetic tests, "the immediate future is more likely to be characterized by confusion," as clinicians and patients seek to make sense of the complex and often incomplete knowledge provided by genetic tests (Welch and Burke 1998).

Even enthusiasts acknowledge that developments in genetic testing pose challenges for health systems and health policy. First, genetic tests are technically complex. While the genetics of rare, single-gene diseases are relatively straightforward, the genetics of common disorders are extremely complex (Collins 1999). Second, the information provided by genetic tests is not easy for clinicians and patients to understand or use; these challenges are exacerbated for tests for common disorders (Welch and Burke 1998). Third, there are not enough genetics specialists to provide genetics services, and primary care clinicians, who are expected to become the chief providers of genetics tests, are not currently prepared for this difficult task (Collins 1999). Fourth, genetic tests pose challenges for adequate evaluation and priority setting and methods for their assessment are still under development (Goel 2001; Subcommittee on Evaluation 2001). Finally, the cost implications of genetic tests are poorly understood. While conjectures about cost increases or cost savings are common (Danzon and Towse 2000), available empirical studies are limited in their scope and adequacy (Giacomini 2001).

The literature on genetic tests offers surprisingly little guidance for assessing the cost implications of predictive genetic tests. Much of the literature on genetics and genetic testing focuses only on the tests and their properties, without assessing in a meaningful manner either how the test can best be deployed in a health care system or how the introduction of the test will affect health care costs. In contrast, the literature on the costs of genetic testing can be divided into two strands. The first attempts to make undifferentiated claims about genetic tests and the "genomic revolution", lacking reference to any specific tests and their properties. This literature is the staple of discussions that appear in the popular media and often includes unsubstantiated forecasts regarding costs. These forecasts tend to predict either that genetic advances in prediction, diagnosis and treatment will bankrupt health care funders or that they will be the saviour of funders by controlling or reducing health care system costs. In any event, they are of little value in understanding how genetic testing may really affect health care costs. The second, and smaller strand, consists of economic evaluations of specific predictive genetic tests applied in narrowly defined circumstances from which it is difficult to generalize to broader system impacts.

This report examines the potential impact of predictive genetic tests and their application as a health care service on health care costs. Their impact on health care costs, of course, depends on a range of factors yet unknown, and it is therefore impossible to predict accurately their cost impact. We therefore attempt to identify key characteristics of predictive genetic tests themselves, of their application as a health care service, and of the information they generate that might change health care decisions and the associated costs. We then use this framework to examine how four specific tests may affect health care costs. Our objective is to lay out a general framework that can help identify the factors determining the cost impact of any given test, how the choices of health system decision makers at all level of the health care system can affect those costs, and to illustrate this with reference to some specific predictive genetic tests.

The report proceeds by first examining characteristics of predictive genetic tests and their application in the health care system (Section 2). We propose three "types" of genetic tests, distinguished by their ability to predict genetically based diseases. We then discuss the characteristics of a genetic test service, which we define as the package of the test technology

plus a target population plus a clinical context [Giacomini, 2001]. The design of the genetic test service determines how any particular genetic test will be used within the health care system. Together, the predictive power of a genetic test and the service context within which it is used provide insight into the costs to the health care system of providing a genetic test itself. Next we integrate these considerations into a discussion of how the introduction of a predictive genetic test service in our health care system might change overall health care costs (Section 3). The cost impact of a genetic test depends on the characteristics of the test, the scope of its application, and on how it changes clinical practice with respect to disease surveillance, disease prevention, and disease management and treatment. In many cases, the cost of the test service itself (often the focus of much concern) makes up only a small part of the change in overall health care costs that flow from its use. Section 4 then extends these ideas to an examination of the potential cost impact of four specific genetic tests by drawing on the existing literature and, for two of the tests, presenting original costing analyses. Finally, in section 5, we discuss some broader issues in how the development and use of predictive genetic tests will affect health care costs, issues that are difficult to integrate into a specific costing exercise.

A few caveats are necessary before beginning. First, our focus is on predictive genetic tests only. There are other uses of genetic tests that we do not consider, whose system impacts may also be significant. Some examples include:

(1) Genetic testing used to guide decisions about reproductive options, including the choice of a partner, the option to pursue or forgo reproduction, or the use of prenatal diagnosis. Together with newborn genetic testing, these are the most widely used genetic testing services. Examples include prenatal screening for Down's syndrome and other chromosomal anomalies, and antenatal carrier screening for recessive conditions such as Cystic Fibrosis.

(2) Genetic testing used to personalize or target approaches to drug therapy to account for the fact that individual responses to drug therapy often vary by genotype (Schmitz, Charalampos et al. 2001) (Epler and Laskaris 2001) (Hess and Cooper 1999) (Larkin 1998). Like predictive genetic testing, "pharmacogenomic" testing is expected to expand as more polygenic pharmacologic effects are identified. (Evans and Relling 1999).

Second, we consider only potential financial cost impacts. We do not examine or attempt to integrate into the analysis the effect of such tests on health or well-being. Accordingly, we are in no way attempting to assess whether a particular predictive genetic test (or class of such tests) should be publicly insured. Any decisions regarding coverage must be based at minimum on a weighing of the costs and the benefits of a test, as well as a range of ethical, legal and other considerations.

Third, in examining the cost impact, our perspective is that of the formal health care system. We do not consider effects on informal care, on broader economic indices such as productivity, or on costs outside the health care system.

2.0 Factors in Assessing Costs of Genetic Test Services

The cost of providing a genetic test is a function of, among other things, the nature of the genetic test; the nature of the genetic test service – or, how the test is used; and how the genetic test information changes clinical practice related to the diagnosis, surveillance, prevention, management and treatment of genetically-related diseases. This section focuses on the first two considerations; the third is discussed in the next section.

2.1 The Nature of the Genetic Test

Predictive genetic tests are not all alike. There is no consistency in the literature about the "types" of genetic tests and different terms are used to describe these tests. Nonetheless, there is a consensus that predictive genetic tests can be distinguished by the extent to which the genetics of the tests adhere to straightforward Mendelian patterns of inhertance, and the extent to which the conditions the test targets are common or rare.

Predictive genetic testing has, to date, focused on relatively rare genetic diseases involving a mutation in a single, highly-penetrant[1] gene. Such tests have the potential to be highly predictive because individuals identified as having the mutation are very likely to get the

[1] Penetrance is defined as the proportion of individuals with the mutation who will develop the disease or disorder in question. For a gene with 80% penetrance, therefore, 80% of the individuals with the mutation will develop the associated disease.

clinical condition. Insofar as predictive genetic testing remains focused on these rare, highly penetrant genetic diseases, its health system impact will necessarily be limited as only a small number of diseases and disorders that follow this genetic pattern -- most diseases and disorders are not strictly genetic.

Many however, advocate for (and expect) a growing role for predictive genetic testing in common, complex disorders. Genes play a role in common disorders such as cancer and heart disease, but identified genes act in concert with other genes, other biological processes and environmental processes. The genetic role is therefore very complex. Multiple genes may be involved, many of which will not be disease-*causing* mutations, but rather the genes act as modifiers in concert with other factors to affect the overall risk of developing what is a multifactorial disease. Because many with the specific mutation will not develop the disease, just as many without the mutation will develop the disease, genetic tests that identify specific genetic risks for multifactorial diseases will *not* be very predictive of those who will eventually develop the disease in question.

We distinguish three types of predictive genetic tests and associated conditions on the basis of their expected (or theoretical) predictive power:

1. *Full Penetrance Genetic Tests* have the potential to be fully predictive tests. They test for genetic conditions where one gene causes the disease in essentially 100% of the diagnosed individuals. All persons with genetic mutation will develop the disease; all those with the disease have the genetic mutation. In this context, the predictive power is limited only by the ability of the test to identify the relevant genetic mutation. The classic example of a full penetrance genetic test is the test for Huntington disease. Huntington disease is a relatively rare, adult-onset genetic disease resulting in neurological deterioration and early death. It is caused by mutations in a single gene that leads to the disorder in virtually 100% of affected individuals. Fully penetrant genetic diseases follow simple patterns of Mendelian transmission. For Huntington disease, which is a dominant disorder, biological children of an affected parent are at 50% risk of inheriting the gene, and therefore, are at 50% risk of developing the disease. Other than in cases caused by sporadic mutations, the persons at risk

of this disease are relatively easy to identify as the disease observes clear patterns of familial transmission.

2. *Predisposition Genetic Tests* have the potential to be highly, but not fully, predictive. They test for genetic conditions where the associated gene or genes are causative of the disease, but not fully penetrant. Individuals identified as having these genes are at high risk (though not 100%) of developing the disease; individuals without the disease-causing mutations are not at risk. Examples include genes that have been identified for highly heritable versions of more common disorders, including BRCA1 and BRCA2 genes in Hereditary Breast and Ovarian Cancer syndrome and mutations in at least 5 mismatch repair (MMR) genes in Hereditary Non-Polyposis Colorectal Cancer Syndrome (HNPCC) (Collins 1999; Rabelo, Foulkes et al. 2001).

3. *Risk Factor Genetic Tests* have only limited predictive power. They test for a genetic factor (or factors) in multifactorial diseases where the gene does not play a definitive role in producing disease. Risk factor tests provide probabilistic rather than deterministic information – the presence of the genetic variant or anomaly does not fully predict disease and the disease can develop in its absence. In theory, risk factor tests could be developed for many known diseases. Information from these tests might be used alone or in combination with information from other genetic or conventional tests to provide risk information to tested individuals, and/or to guide therapeutic interventions.

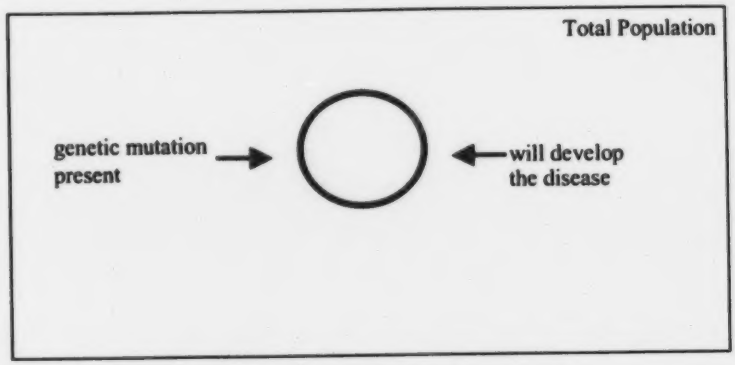
These distinctions are not watertight, but they do capture some central characteristics of predictive genetic tests.

The relationship between a person's genetic characteristics and their disease state for these three types of tests can be illustrated using Venn Diagrams (Figure 1). In Figure 1(c), which depicts this relationship for risk factor tests, the circle to the left with a thicker border represents the subset of the population with the genetic mutation of interest. The circle to the right with a thinner border represents the subset of the population who has (or will develop) the disease in question. In the diagram, area A represents those with the genetic mutation who will never develop the disease, area B represents those who will develop the disease and who lack the

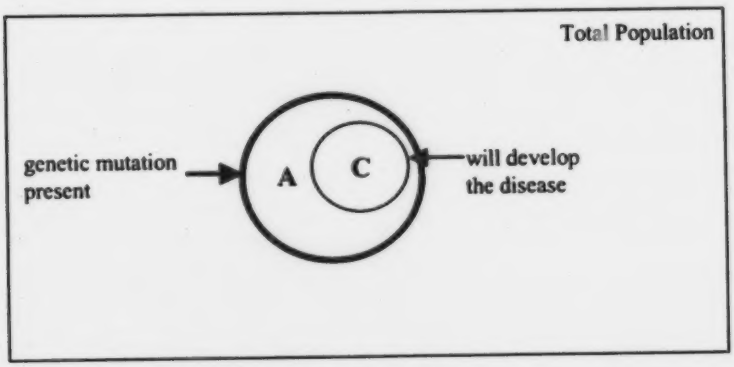
genetic mutations and area C represents those with the genetic characteristics who will develop the disease. The predictive power of a test depends in part on the size of area C relative to A. For risk factor tests, C tends to be small relative to A because the genetic characteristic is only one of many determinants of the disease and the genetic feature per se does not cause the disease; it is simply a contributing factor working in interaction with other factors. In contrast, for predisposition tests (Figure 1(b)), many of those with the genetic mutation will get the disease while those without the mutation will not. Hence, there is no area B. In the case of full penetrance tests (Figure 1(c)), the two circles fully coincide.

No medical test, genetic or otherwise, is perfect at identifying who has or will eventually develop a disease and who will not. The notion of predictive power, or test accuracy, can be given more precision through the concepts of test sensitivity and specificity (Sackett, Haynes et al. 1991). The sensitivity of a test is defined as the probability that a test result will be positive in a person with the genetic mutation in question. Specificity is defined as the probability that a test result will be negative in a person who does not have the mutation in question. The higher the sensitivity and specificity, the better the test is in distinguishing those people with the mutation of interest from those without it

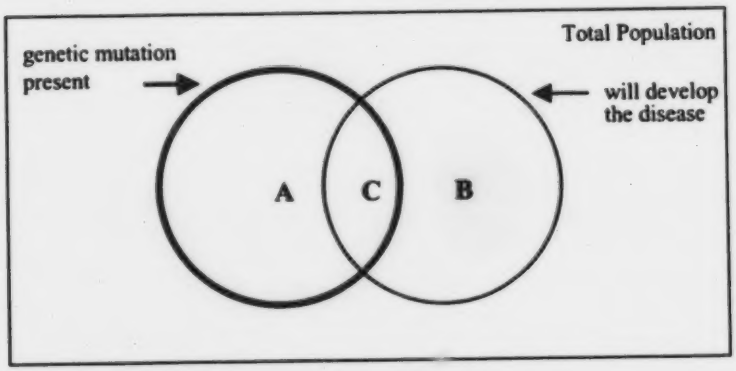
Figure 1: Three Types of Predictive Genetic Test:



(a) Full Penetrance Predictive Genetic Tests



(b) Predisposition Predictive Genetic Tests



(c) Risk-Factor Predictive Genetic Tests

For predictive genetic tests, predictive power in terms of identifying those who will or will not develop the disease in question is a function of, among other things, two related phenomena:

1. Analytical validity: the ability of a test to identify whether a specific genetic mutation is present, i.e., test sensitivity and sensitivity (Secretary's Advisory Committee on Genetic Testing (SACGT) 2000);

2. Clinical validity: the degree to which the identified mutation predicts the onset of a clinical disease state, i.e., pentrance (Secretary's Advisory Committee on Genetic Testing (SACGT) 2000).

Many technical and theoretical issues impinge on the predictive power of any particular gene test. As the above discussion has emphasized, even a test with high analytic validity will have poor overall predictive power of it has poor clinical validity (e.g., risk factor tests). A highly predictive test requires that the test accurately distinguishes those with and without the mutation (an ability that may change over time with technological development) and that the mutation is strongly linked with the disease (a fixed biological relationship). The real world analytical validity of a test can vary across laboratories and procedures used to conduct the test, and will only approximates the analytical validity attained under ideal conditions. Each gene can have many mutations, not all of which are fully described or understood. For example there are over 900 reported mutations for CF, which is a relatively simple genetic disease (Grody and Desnick 2001). In addition, the capacity of any laboratory to test for various loci and mutations can be limited both by technical ability, by cost and by other service constraints. Where patents on genetic tests exist, and where they are exercised in restrictive or exclusive ways (OECD 2000) the ability of a laboratory to use different testing protocols may also be constrained.

Clinical validity is not always straightforward, as many even theoretically *simple* genetic diseases (e.g., fully penetrant or predisposition type genetic diseases) have very complex genetics. Some genetic diseases are associated with multiple genes. Test accuracy is thus a function of the ability to test for all of the known genes. In addition, there may be as-yet-unidentified genes that are believed to be predictive of the condition (e.g., the expected BRCA3,

etc., genes). Clinical validity is thus compromised by inadequate knowledge of the genes involved. Further, knowledge of clinical validity is a function of the adequacy of genetic epidemiology – knowledge of the incidence of the allele and its associated clinical risks in populations. Early investigations of genes discovered to be disease inducing tend to overestimate the risk of the disease (e.g., BRCA1) (Welch and Burke 1998). This transpires because early studies are conducted among exceptionally high-risk individuals. As the tests are used in larger target populations (e.g., beyond the biological families used to first identify the locus), the predictive power of the test is generally shown to be reduced. The predictive power even of fully penetrant or predisposition tests in individuals who lack the associated clinical risk factors, such as family history, is often not well known.

Finally, predictive genetic tests often identify risks for more than one disease (Evans, Skrzynia et al. 2001; Miller and Giacomini 2001). Any single gene can affect several different biological processes. This heterogeneity often produces a syndromes rather than disease. Cystic Fibrosis for example, involves defective electrolyte transport in epithelial cells as a result of mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. This leads to abnormally viscid mucus secretions (Grody 1999), with pulmonary complications and pancreatic insufficiency as the most serious clinical consequences. The heterogeneity of the profile of genetic disease becomes more challenging for predictive genetic tests where the onset of disease is in the future. For many of these syndromes there is a primary disease, which is often what the syndrome is named for, but there may also be several auxiliary diseases. For example, some predictive genetic tests for familial cancer syndromes place people at risk for *many* cancers. Yet knowledge about the degree of risk is often variable for these different outcomes (Evans, Skrzynia et al. 2001); indeed, some auxiliary risks may have been masked by the mortality caused by the primary disease, and only become apparent as clinically significant risks when survival increases as a result of screening and other interventions for the primary disease.

2.2 The Nature of the Genetic Test Service

The costs of a genetic test are a function not simply of the test characteristics, but of how the test is used – in other words, the genetic test *service*.

One of the key variables defined by a genetic test service is the target population. To some extent, predictive genetic tests have "natural" target populations. Full penetrance and predisposition genetic tests are appropriate for individuals at risk of those specific genetic diseases. These individuals are generally identified by family history and, where available, the clinical hallmarks of the condition. Case finding for these conditions generally involves the identification of a proband – the individual who is first recognized as being at risk of a genetic disease, often because of the development of the disease, and the subsequent follow-up of biological family members. Screening programs for these diseases are generally highly targeted. By contrast, the "natural" target population for risk-factor genetic tests is potentially much broader. These genetic tests assess genetic risk factors for sporadic (non-hereditary) conditions. Thus, these tests may be usable for population screening.

The actual target populations for various genetic tests will vary depending on such issues as test capacity and options for clinical management, including surveillance, prevention, management and treatment. It will also vary as a function of clinical and patient interest and demand. Policy makers often face many options for the appropriate use of predictive genetic tests.

The identification of a target population involves several considerations. Some genetic diseases, for example, lack a clinical hallmark, so family history is used to identify a target population. Scientific consensus is sometimes lacking, however, about appropriate criteria to identify a suspect family history and such criteria can be narrowly or broadly defined. Moreover, sometimes non-genetic tests can be used as initial screening devices prior to the use of a molecular genetic test, and decisions need to be made about the merits of these protocols. For risk factor tests, options are even broader. A risk factor test result can, for example, be used as a single test result to assess risk, or combined with the results of other risk-determining tests and assessments (including genetic and conventional tests) to determine an individual's overall risk.

The manner in which tests are made available to the population will affect clinician and patient behaviour. Tests could be provided essentially upon request (either by clinical referral or directly by an individual) only through specialized genetic services or some tests could be provided by primary care physicians and might be offered to patients as part of a regular clinical

visit. Under either scenario, issues related to genetic counselling and informed consent will have an impact on patient comprehension and test uptake (Marteau and Croyle 1998). Tests that are directly marketed to the consumer (most likely risk factor tests) are likely to have a variety of system impacts. At a minimum, some form of regulation will likely be necessary to ensure that marketers meet appropriate standards of accuracy and informed consent (e.g., (Advisory Committee on Genetic Testing 2000)).

Finally, a range of clinical management options are often available, including surveillance, prevention and treatment. The phenomenon of genetic heterogeneity exacerbates the challenge of designing appropriate clinical management protocols. In these cases, decisions have to be made about which clinical characteristics to count in identifying the target populations, which diseases to screen for in a systematic fashion, and what preventive, management and treatment options should be recommended, especially given the often variable knowledge about the different diseases for which an individual is at risk.

2.3 Classifying Risk Status through Predictive Genetic Tests

When a predictive genetic test is used in practice, it will divide the population tested into two groups: those with a positive test result and those with a negative test result. But, as emphasized above, the tests are not perfect either in identifying the genetic mutation or in predicting who of those with the mutation will develop the disease. Hence, some of those with a positive test result will never develop the disease and some of those with a negative test will eventually develop the disease. This is particularly the case for broad risk factor testing that can only indicate a heightened risk for the disease. Because the test result may change health care seeking behaviour, to understand the impact of the introduction of a genetic test service on health care costs it is useful to further divide those with positive and negative test results into the following: (1) true positives (people with a positive test score and who would have gone on to develop the condition); (2) true negatives (people with a negative test score and who would have not developed the condition); (3) false positives (people with a positive test score but who would not have gone on to develop the disease); and (4) false negatives (people with a negative test result but who would have gone on to develop the disease). At the time the test is administered,

of course, we know neither which of the positives are true and which are false, nor which of the negatives are true and which are false.

The extent to which a given application of the test classifies individuals into each of these categories is crucial in understanding how the introduction of a test will change the behaviour of individuals and clinicians compared to a world without the genetic test service. An individual with a false positive genetic test result who would never have developed the disease, for instance, may unnecessarily increase use of surveillance and prevention services because the test tells them they are at high risk. But, by correctly classifying a person as low risk, a true negative may save costs for the same services if a person might otherwise have sought them out in the absence of the test result. In general, if decisions with respect to health care utilization for surveillance, prevention, or treatment are influenced by the test result (as they should be: otherwise, why do the test?), then the effect of the genetic test on health care costs (both positive and negative) depends on how people in each of the above four categories change consumption patterns and the distribution of test results across the four categories.

To fix these ideas concretely before discussing specific predictive genetic tests, suppose we have the following: a population of 10 million persons; a genetic test for a mutation with 100% penetrance for which both the test sensitivity and specificity are 0.95. (This is a *very* good test: The specificity and sensitivity are in the range found only for some full penetrance tests and better than most current predictive genetic tests). Assume also, that the test is used to predict those at risk for the population prevalence is 0.05. Assume first that we target this test on a high-risk subset of the population (identified by non-genetic information and including all 500,000 who will eventually get the disease) so that lifetime prevalence among this high-risk target group is 0.40. The program would therefore test 1.25 high-risk individuals and categorize them as follows: 475,000 would be true positives, 712,500 would be true negatives, 37,500 would be false positives, and 25,000 would be false negatives (Table 1 column A). The testing service correctly identifies 95% of both those who will get the disease and those who will not; false results constitute 5% of all test outcomes. False positives constitute less than 8% of all positive results and false negatives less than 4% of all negative results. In contrast, if we were to apply even this very good test population wide, the results would be quite different. A population–

wide screening program would classify the 10 million people as follows: 9.5 million would be classified correctly as either a true positive (475,000) or a true negative (9.025 million); 500,000 individuals would be misclassified as a false positive (475,000) or as a false negative (25,000)(Table 1, column B). The number of true positives (475,000) and the rate of false results (5% of all test results because sensitivity and specificity are unchanged) under both the targeted and population-wide screening programs remain the same. But because the test is so widely applied under the population-wide program (and thus the prevalence of the condition is reduced), fully half of the positive test results are false. To the extent that those with a positive result consume additional health care services they otherwise would not have, the broader screening program has not only increased the cost of providing the test service, it has increased other system costs without identifying any additional cases of the disease.

To predict the impact of a test on health care costs, it is therefore necessary but insufficient to assess how good a test is – it is crucial to also consider how it will be implemented and the rates at which the testing program will generate true and false results in the population, with the attendant change in health care utilization patterns for each type of recipient.

Table 1: Effect of Screening Approach and Test Characteristics on Classification of Those Tested

	Column A	Column B	Column C	Column D	Column E	Column F
	Good Test and Targeted Screening at High-risk Populations	Good Test and Population-wide Screening	Low Sensitivity and Targeted Screening at High-risk Populations	Low Specificity and Targeted Screening at High-risk Populations	Low Sensitivity and Population-wide Screening	Low Specificity and Population-wide Screening
Population Tested	1,250,000	10,000,000	1,250,000	1,250,000	10,000,000	10,000,000
Prevalence in tested population	0.40	0.05	0.40	0.40	0.05	0.05
Sensitivity	0.95	0.95	0.60	0.95	0.60	0.95
Specificity	0.95	0.95	0.95	0.60	0.95	0.60
Distribution of Those Tested						
True Positive	475,000	475,000	300,000	475,000	300,000	475,000
True Negative	712,500	9,025,000	712,500	450,000	9,025,000	5,700,000
False Positive	37,500	475,000	37,500	300,000	475,000	3,800,000
False Negative	25,000	25,000	200,000	25,000	200,000	25,000
Total	1,250,000	10,000,000	1,250,000	1,250,000	10,000,000	10,000,000

The above test was highly predictive by current standards. We can also assess the impact of lowering the clinical sensitivity or specificity to levels more commonly encountered. If we assume a test sensitivity of 0.6 (this is still well above the sensitivity of many risk-factor tests) and a targeted screening program, we see that the test is less accurate at identifying those with the disease. Out of a population tested of 1.25 million people, the number of true positives falls from 475,000 when sensitivity was 0.95 to 300,000 when sensitivity is 0.6 (Table 1,column C). The number of true negatives and false positives remains unchanged, but the number of false negatives increases from 25,000 to 200,000 (i.e., lower sensitivity causes the false negatives to increase by exactly the decrease in true positives). Analogously, lowering specificity while sensitivity remains at 0.95 (Table 1, column D) decreases the test's ability to identify those who will not develop the disease, causing the number of true negatives to fall (712,500 to 450,000) and the number of false positives to increase (37,500 to 300,000). The same patterns occur for

the case of population screening (Table 1, columns E and F), though of course the numbers (and the associated cost implications) are much larger.

The above highlights how the test characteristics interact with the scope of the test's application to affect how many true positive, true negative, false positive and false negative results are generated. As alluded to above, the cost implications of these differing patterns of results then depend on how utilization patterns are changed for each type of test result. Will those with false negative results forgo otherwise effective preventive treatments, thereby raising eventual treatments costs? Will those with false positive results take up surveillance and preventive care that is unnecessary and which they would not have consumed in the absence of the test result? We now examine in more detail cost implications for those who receive a test.

3.0 Cost Implications of the Results of Genetic Tests

Our concern is how the introduction of predictive genetic tests will affect health care costs. We must therefore assess what costs would be in a world without the newly developing predictive genetic tests and what costs will be with such tests.

The cost implications of the use of genetic tests, therefore, depends on what each person does based on the information provided by the genetic test and what they would have done in the absence of this information. Table 2 outlines some possible cost patterns with respect to the cost of the test itself, the cost of surveillance, the cost of prevention and the costs of treatment for those who develop the disease. These are simplified illustrations of some of the basic patterns that might be observed; the table is not exhaustive of all possibilities.

Table 2: Cost Implication of Predictive Genetic Tests

Population Who Receives the Test		**Types of Costs to Health Care System**			
Disease Status	**Post-Test Status**	***Costs Associated with Case-finding when practice is...***	***Costs Associated with Surveillance when current practice is...***	***Costs Associated with Prevention when current practice is...***	***Costs Associated with Treatment when current practice is...***
		a. no current test *b. genetic test replaces current test* *c. genetic test in addition to current test*	*d. no surveillance for anyone* *e. surveillance for high risk HR) individuals* *f. surveillance for general population*	*g.. no preventive treatment* *h. preventive treatment for high risk (HR) individuals* *i. preventive treatment for general population*	*j. intervention specific to condition*
Compared to the current world without a genetic test, the introduction of a genetic test will have the following effects on health care costs for each identified type of individual for each alternative type of current practice pattern:					
Those with the Disease (or who will get it eventually)	**True Positive**	a. increase b. increase or decrease depending on relative costs of tests c. increase	d. no change e. previous HR: no change previous LR: increase f. no change or increase if surveillance intensified	g. no change h. previous HR: no change previous LR: increase i . no change or increase if treatment intensified	j. reduced if prevention effective or early detection less costly to treat
	False Negative	a. increase b. increase or decrease depending on relative costs of tests c. increase	d. no change e. previous HR: decrease previous LR: no change f. decrease	g. no change h. previous HR: decrease previous LR: no change i. decrease	j. no change or increased if failure to detect early increases costs
Those without the disease (or who will never get it)	**False Positive**	a. increase b. increase or decrease depending on relative costs of tests c. increase	d. no change e. previous HR: no change previous LR: increase f. no change or increase if surveillance intensified	g. no change h. previous HR: no change previous LR: increase i. no change or increase if treatment intensified	j. no change
	True Negative	a. increase b. increase or decrease depending on relative costs of tests c. increase	d. no change e. previous HR: decrease ...previous LR: no change f. decrease	g. no change h. previous HR: decrease previous LR: no change i. decrease	j. no change

Costs of Testing Itself: The introduction of a genetic test will unquestionably increase the cost of diagnostic/predictive testing in two situations: if there is no current predictive/diagnostic test in clinical practice (option a in Table 2) or if the genetic test is used in addition to any existing test protocols (option c in Table 2). If the genetic test replaces an existing test (option b), then the net effect on costs depends on the relative cost of the genetic and non-genetic test. Even if it replaces an existing test and is of lower per-unit cost, if it is (wisely or unwisely) applied more widely than the current test, aggregate costs of testing could increase. Behavioural responses by individuals and clinicians play a determining role in the cost impact of a new, lower cost, "substitute" test.[2] We discuss some of these issues in more detail below.

Cost of Surveillance: Surveillance refers to clinical activities undertaken to monitor the disease state of individuals (especially those at high risk) in the hope of detecting at an early state any developing disease. If no surveillance is carried out under current clinical practice (option d), the introduction of the test will lead to no change in costs associated with surveillance -- if there is no effective surveillance interventions even the results of a good test should not induce such activity. If, in contrast, current practice includes a broad, population-wide surveillance protocol (option f), then the introduction of a predictive genetic test would likely reduce total surveillance costs. if those with a "negative" test discontinue the surveillance protocol because they are at low risk. The more complicated context to predict is one in which current practice is a surveillance protocol for individuals identified as high risk based on non-genetic information. Surveillance costs in this situation would likely not change for two types of individuals: a person who would have been classified as high risk without the genetic test and for whom the genetic test is positive, and a person who would have been classified as low risk without the genetic test and for whom the test is negative. Surveillance costs would likely decrease for those individuals who would be classified as high-risk based on non-genetic information who have a negative test result (and who therefore reduce surveillance activities). Likewise, costs would likely increase for those who would be classified as low risk based on non-genetic information and who have a positive test result (which induces them to increase surveillance activities).

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[2]The analogy to home care and hospital care is pertinent. Home care, when substituted for hospital care, is often of lower cost per case, but once introduced, many people use home care who would not have been hospitalized,

Prevention Costs: The same general patterns found for surveillance costs follow for the costs of prevention. If there is no preventive treatment (option g), then introduction of the test does not change costs of prevention. If prevention would have been taken up by a large portion of the population (option i), then again the test may well reduce such costs as those with a positive test result reduce preventive activities. Finally, in those situations in which current practice prescribes preventive treatment only for individuals classified as high risk based on non-genetic information (option h), the overall effect of the test on prevention costs depends again on the relationship between the test result and their non-genetic high-low risk status. Prevention costs would likely decrease for those individuals who would be classified as high risk based on non-genetic information who have a negative test result (and who therefore reduce preventive activities). Likewise, costs would likely increase for those who would be classified as low risk based on non-genetic information and who have a positive test result (which induces them to increase prevention activities.

Treatment Costs: The last type of cost incurred is treatment costs for those who develop the condition. The introduction of the genetic test will reduce treatment costs for true positives if an effective preventive treatment is available or if early detection reduces treatment costs. It may increase costs for false negatives if the test result causes them to forego an effective surveillance regime or preventive activity and/or if it induces delay in seeking treatment. There is no change in treatment costs for those who never develop the disease.

3.2 Putting it all Together

We are now in a position to put all of this together to identify how patterns of test characteristics, genetic testing programs, and cost situations interact to determine the impact of the introduction of a test on health care costs. Table 3 lists some characteristics of predictive genetic testing scenarios that are likely associated with lower health care costs following the introduction of a predictive genetic test and those associated with higher health care costs. The characteristics listed in Table 3 describe tests that will increase or decrease health care costs per

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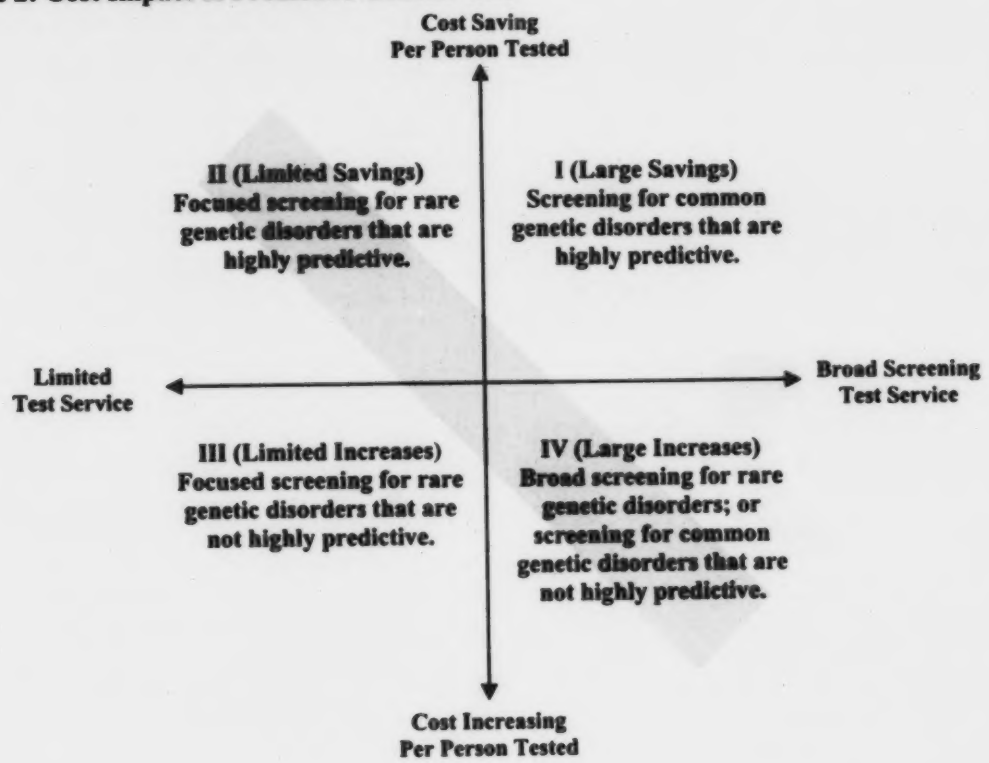
increasing total system costs.

person tested. Figure 2 plots genetic testing services along the dimensions of the scope of testing offered and the cost impact per test. Tests that reduce overall health care costs per individual tested lie above the horizontal access; those that increase costs like below. Those services that apply to highly limited populations lie to the left of the vertical axis, and will have modest impact on overall health care costs corresponding to their limited scope. Those tests that are applied broadly—to the right of the horizontal access—will have correspondingly large financial impacts. The gross financial impact from testing services ranges from significant cost savings to significant cost increases as one moves counter-clockwise from quadrant I through IV. The shaded slope illustrates the notion that, those genetic test services that have favourable cost-impact per person tested tend to be focused screening programs. As genetic testing services for rare familial disorders are extended to broader applications, however, the cost-impact tends to become less favourable.

Table 3: Characteristics of Testing Scenarios that Decrease or Increase Health Care Costs

		Cost Decreasing	Cost Increasing
Gene Characteristics		High penetrance	Low penetrance
Test Characteristics		• high sensitivity • high specificity	• low sensitivity • low specificity
Test Service Characteristics		• low-cost ability to target test at high-risk persons	• high cost of targeting • broad, population testing
Health Care Costs	**Genetic Test**	• low cost • in absolute dollars • relative to current non-genetic test	• high cost • in absolute dollars • relative to current non-genetic test
	Surveillance	• prevents uptake of high-cost unnecessary surveillance • induces uptake of effective, low-cost surveillance that prevents downstream treatment costs	• induces uptake of high-cost unnecessary or ineffective surveillance • inhibits uptake of effective, low-cost surveillance that prevents downstream treatment costs
	Prevention	• prevents uptake of unnecessary preventive care • induces uptake of effective, low-cost preventive care that prevents downstream treatment costs	• induces uptake of high-cost unnecessary or ineffective surveillance
	Treatment	• early identification prevents the need for high-cost treatment	• information provided by test has no impact on (or in some way) increases treatment costs

Figure 2: Cost Impact of Predictive Genetic Test


Cost Saving
Per Person Tested
II (Limited Savings)
Focused screening for rare genetic disorders that are highly predictive.
I (Large Savings)
Screening for common genetic disorders that are highly predictive.
Limited
Test Service
Broad Screening
Test Service
III (Limited Increases)
Focused screening for rare genetic disorders that are not highly predictive.
IV (Large Increases)
Broad screening for rare genetic disorders; or screening for common genetic disorders that are not highly predictive.
Cost Increasing
Per Person Tested

A dream predictive genetic test for a health care funder, which would generate large savings to the health care system, is a test that:

- is for a gene that is highly penetrant for a condition of moderate to high prevalence
- has high sensitivity and specificity,
- can easily be targeted at high-risk individuals at low-cost
- is low-cost and replaces a higher cost non-genetic test currently in use
- either prevents the uptake of marginally effective surveillance or preventive care or which induces the appropriate uptake of effective surveillance or preventive care that avoids the need for large treatment costs.

In contrast, a nightmare test for a health care funder, which would generate large cost increases to the health care system, is a predictive genetic test that:

- is for a gene that has low penetrance for a condition of high prevalence
- has low sensitivity and specificity,

- is applied on a population basis
- has a high cost to administer and/or is used in addition to any non-genetic test currently in use
- either:
    - false negatives inhibit the uptake of effective surveillance or preventive care that would avoid high treatment costs;
    - false positives induce the uptake of surveillance or preventive care;
    - true positives induce the uptake of ineffective surveillance or preventive care

Because the of potential application is so broad, risk-factor tests have the potential to change the health care seeking (providing) behaviours of large numbers of individuals (providers), thereby generating the greatest range of cost impacts. Risk factor tests bring to mind Longfellow's nursery rhyme: "When she was good, she was very, very good. But when she was bad, she was horrid." For example, a risk-factor test for coronary artery disease could result in large numbers of people taking cholesterol lowering drugs for decades. Even if reasonably effective, such tests impose large costs in the near future to avoid treatment costs (and health benefits) long into the future.

Their potential for large cost impacts demands particular scrutiny and care in designing the programs through which they will be delivered. Even good tests, when misapplied, can generate large cost impacts. These tests may also pose some of the greatest challenges, as they are the type of test most likely to me marketed directly to consumers and most likely to he applied in a much broader range of situations than they might initially be approve for.[3]

In contrast, because they are generally associated with rare genetic disorders, the narrowest range of cost impacts arise with fully penetrant, single-gene tests. Even when such test generate large savings in each individual tested, the total costs savings are small; similarly, even when such a test increases costs, the total cost increase is small. Again, we will examine

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[3]There is a direct analogy to the experience with many drugs, which gain approval for use in a narrow set of circumstances according to well-defined criteria but which, once on the market, are prescribed for a wide range of situations not initially intended.

in detail in the next section, a predictive genetic test for Familial A P, a predictive genetic test of this type.

Finally, in between these two extremes are the susceptibility predictive tests. Like fully penetrant tests, they often have high predictive power, but like risk factor tests, their potential scope of application is sometimes quite broad. We will discuss in more detail two such tests in the next section: a predictive genetic test for HNPCC, a particular form of colorectal cancer, and a predictive genetic test for HH.

Two related points are worth emphasizing here. The first is that in many cases the costs of testing is a relatively small contributor to the health care cost impact of a genetic test service. Funders who do not pay for the test itself will bear costs of surveillance, prevention, and treatment when tests are provided through other sources. Second, population targeting —as much or perhaps even moreso than the technical "accuracy" of the test — will profoundly influence the proportion of accurate results in a given test population. Follow up on inaccurate results can create a great deal of wasteful health spending. When these two points are taken together, it becomes apparent that health care funders have an interest in controlling the use and targeting of new predictive genetic tests.

4.0 Analyses of the Costs of Genetic Testing Services

We conducted a search to find literature on the costs and cost-effectiveness of predictive genetic testing services. In November 2001 we searched a number of databases for articles containing one of a variety of cost terms (e.g., "cost," "cost-benefit analysis," or "cost-effectiveness") and one of a variety of genetic testing expressions (e.g., "genetic testing" or "genetic screening"). The databases searched included Medline, HealthStar, EBM Reviews, Cochrane Database, ACP Journal Club, DARE, CANCERLIT, Applied Science & Technology Index, EconLit, Social Sciences Index, and PubMed. We searched for papers published 1996 to present. In total, 340 candidate articles were identified, the abstracts of which were reviewed to determine appropriateness to this study. Seventy-six articles were deemed appropriate methodolgical or empirical works; thirty-two of these contained (some form of) an economic

evaluation of genetic tests, screening programs, or pharmacogenomics. Although important in terms of methodological and theoretical considerations, analyses pertaining to the prenatal diagnosis of a number of disorders (11 of 32 articles) and pharmacogenomics (4 of 32) are outside the scope of this review of economic evaluation of predictive genetic tests.

Topic	Number of Economic Evaluations
Hereditary Hemochromatosis	4
HNPCC	2
FAP	2
Cancer	3
Prenatal Diagnosis	11
Pharmacogenomics	4
Miscellaneous	7

The quality of the economic literature on genetic testing is variable. Those studies that were rigorous in their methodology and data collection tended to apply to genetic testing for rare hereditary disorders in a highly specific context—e.g., based on data or experiences in particularly laboratory settings (Bapat, Noorani et al. 1999). Consequently, generalizations from these studies must be made with caution. Those analyses that applied to broader testing possibilities were highly hypothetical in their assumptions about the structure, uptake, cost, and impact of genetic testing services—this included assessments of predictive genetic testing for entire populations (Brown and Kessler 1996; Adams and Valberg 1999). The reliance on assumptions is a necessity given the evolving nature of genetic technologies and the absence of real-world experience with population-wide applications.

Because of the diversity of the underlying tests, scope of study and contextual settings, generalizations from the economic literature on predictive genetic tests are difficult to make. One clear trend in the findings, however, it is that genetic testing services targeted to high-risk families prove to be more cost-effective than genetic testing services applied to broad populations. But this may simply reflect the fact that the published literature is dominated by studies of relatively rare genetic disorders of a familial nature.

What follows is a review of salient features of the costing analyses for four predictive genetic tests: those to predict familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer, hereditary hemochromatosis, and late onset Alzheimer's disease. See Appendix A for more detailed reviews of the genetic tests. The discussions of familial adenomatous polyposis and Alzheimer's disease are based on our original costing studies; the discussion of hereditary nonpolyposis colorectal cancer and hereditary hemochromatosis are based on the existing published literature. .

4.1 Familial Adenomatous Polyposis

Familial adenomatous polyposis (FAP) is a rare hereditary syndrome caused by mutations in a single tumour-suppressing gene. Individuals with FAP develop hundreds of polyps in the colon at an early age and are nearly certain to develop colorectal cancer by the age of 50.

Genetic testing services for FAP fall into the category of full penetrance predictive testing services. Tests available are quite sensitive, specific, and are highly predictive. Methods commonly used to detect FAP identify genetic mutations in approximately 75 percent of FAP patients.

Because FAP is extremely rare—with an incidence of approximately 1 in 10,000—population screening is not recommended. The costs of such a program would not likely justify the findings. Standard genetic tests for FAP with sensitivity of 75 percent cost $1,297 in Ontario (Ontario 1999). The expected cost of detecting one case of FAP through population genetic screening would therefore be approximately $17 million [$1,297*(10,000/0.75)]. Perhaps because of the magnitude of program costs involved, no studies have been conducted on the economics of population screening for FAP.

Unlike the general population, first-degree relatives of individuals who have FAP are at a high risk (a 50 percent chance) of inheriting the disease. Because of this high risk, relatives of individuals with FAP should undergo annual or biannual colonoscopic surveillance to detect polyps in the early stages of development. Their early removal procedure can delay the onset of cancer, preserving affected individuals' quality of life in the interim. Without a means of identifying those who will actually get the disease, this surveillance strategy is essentially carried

out for a high proportion (50 percent) of false-positives: family members who do not actually have the FAP syndrome.

Because of its potential to identify true-negatives, genetic testing for first-degree relatives of individuals with FAP may prove to be a cost-saving policy. Relatives for whom the FAP mutation can be ruled out do not require colonoscopic surveillance because they will not develop the disease. Two studies have shown that genetic testing for individuals with FAP and their relatives has the potential to generate savings that exceed the costs of testing (Cromwell, R.D. et al. 1998; Bapat, Noorani et al. 1999). Critical variables in these assessments include the cost of the genetic tests, the cost of colonoscopic surveillance programs, the number of first-degree relatives, and the sensitivity of the genetic screening program (Cromwell, R.D. et al. 1998; Bapat, Noorani et al. 1999).

4.1.1 Costing Analysis

We illustrate the issues involved with genetic testing for persons at risk of FAP by extending and updating a previously published study conducted by Bapat and colleagues (Bapat, Noorani et al. 1999). We compare the costs of involving a "genetic testing" strategy against a strategy involving "conventional clinical surveillance" for all first-degree relatives of patients with FAP. This cost analysis was conducted from the perspective of the Ontario Ministry of Health and all costs are expressed in 2001 dollars. Details concerning the methodology, data, and sensitivity analysis are contained in Appendix B.

The method of analysis used here, as in the other studies of FAP testing (Cromwell, R.D. et al. 1998), is a decision analytic model of surveillance under the two general strategies. The model is illustrated in Figure 3. The starting point for the model for both strategies is the proband: a patient presenting with clinically diagnosed FAP, whether that be through family tracing initiatives or through symptoms with subsequent clinical investigations. The model compares the cost of screening immediate family members using conventional screening guidelines versus an alternative test and screen approach based on the outcomes of a genetic test on the proband and on family members.

Figure 3: Decision Analysis Model for FAP Scenarios

Conventional clinical screening. The conventional screening approach for immediate family members of FAP patients involves colonic examinations repeated at regular time intervals. Guidelines for screening asymptomatic high risk FAP family members were established by an international consortium which recommended initiation of flexible sigmoidoscopy from age 10 onwards repeated every 2 years until the age 40 and every 3-5 years thereafter until age 60 (Bulow, Burn et al. 1993). For the present study we assumed that conventional clinical screening of first-degree relatives of patients with FAP would consist of a baseline flexible sigmoidoscopy starting at age 10 with a repeat screen every 2 years to age 35, then every 4 years until age 50.

Both the conventional screening and genetics testing scenarios required information about the number of first-degree family relatives and the age distribution of these relatives at the time the FAP patient first presents for clinical screening or genetic testing. Information for these variables was obtained from the Gastrointestinal Cancer Registry located at the Mount Sinai Hospital at the University of Toronto. From the database, based on 257 FAP registered families, the average number of first-degree relatives of FAP patients is 6. The proportion of first-degree relatives of FAP patients who are between the ages of 10 and 20 years is 60%, between the ages 20 and 30 years is 20%, and between the ages of 30 and 40 years is 20%.

Genetic testing. In the "genetic testing" scenario, a genetic test is conducted on the proband and, if positive, on first-degree relatives. Colonoscopic surveillance is then required for the proband and only those relatives for whom genetic tests results are positive or inconclusive. The sensitivity of the genetic testing algorithm used on the proband in this model was based on findings from the Mount Sinai Hospital. Gene mutations are identified in approximately 74 percent of FAP families using the testing protocol. The cost of the test is $1,297 based on current reimbursement by the Ontario Ministry of Health (Ontario 1999). If the proband's mutation is not found, all first-degree relatives of the proband would have to come in for regular clinical screening. This is because an inconclusive finding for the proband implies that tests for relatives will be inconclusive: true-positives and true-negatives cannot be established unless the particular genetic mutation of the proband is found.

If the genetic test finds the proband's mutation, we assumed that all first-degree family members would come in for genetic counseling and testing. Because the location of the potential mutation is known in these cases, the sensitivity of tests for family members is assumed to be 100 percent, and the test cost is assumed to be $457—much lower than the cost of the proband testing algorithm (Ontario 1999). Since first-degree relatives of affected individuals have a 50 percent pre-test risk of inheriting the disease, half of the first-degree family members tested will be true-positives. If a mutation is found in the family members, they enter the conventional colonoscopic surveillance for FAP patients. If the mutation was not found in the first-degree family member no surveillance is warranted.

Avoiding the cost of surveillance for first-degree family members confirmed to be true-negatives is the primary financial advantage of the genetic testing strategy. This model essentially tests whether the reduction in surveillance costs induced by true-negative findings more than offsets the up-front cost of the genetic testing service.

4.1.2 Results

After accounting for the number of first-degree family members, the age distribution of first-degree family members, the age-dependent clinical screening profiles, and discounting of future costs at a rate of 5% per year, the expected cost of the conventional surveillance strategy

for FAP is estimated to be $9,607. By comparison, taking into account these sure factors plus the cost of the testing service, the expected cost of the genetic testing strategy is estimated to be $8,238. Thus, the cost savings to the health care system from avoided surveillance for true-negative family members detected under the genetic testing strategy more than offset the additional cost of the genetic tests themselves. The net savings per FAP family was $1,369 ($9,607-$8,238). This means that for each new FAP family, the Ontario Ministry of Health would expect to save $1,369 on average by adopting a policy of genetic testing before engaging in conventional surveillance for FAP families. There may be as many as 150 families in Ontario with a history of FAP. Consequently the net savings to the province from these testing services would be in the ball park of $200,000.

The results of the costing analysis proved to be robust to realistic changes in two of the variables that were determined to be important in previous assessments: the cost of the genetic tests and the sensitivity of the genetic screening program (Cromwell, R.D. et al. 1998; Bapat, Noorani et al. 1999). However, the results are sensitive to reasonable cost estimates for the clinical surveillance and the assumed family size. If the cost of colonoscopic surveillance drops below $200 (from $281.56 in the base case), or if the number of family members is less 3.8 on average, the genetic testing model is no longer less costly than the conventional surveillance model. Details concerning these sensitivity analyses are found in Appendix B.

As with previous studies of genetic testing for FAP families, our model has several noteworthy limitations. First, this is an analysis of costs only and no relevant patient outcome measures, such as quality of life, have been included. Second, the analysis was conducted from the perspective of the Ontario Ministry of Health. A more comprehensive analysis would include costs to patients and other sectors of the economy. Third, the current model stops tracking costs once the patient develops polyps. A more complete cost analysis would include treatment for polyps (e.g. laser removal, or surgery to remove colon) and other auxiliary diseases and the long-term costs and consequences of these treatment alternatives.

Neither this study, nor previous economic analyses, addresses the uptake of genetic tests or the compliance with colonoscopic surveillance. It is highly unlikely that the uptake of genetic testing services will be 100 percent, as assumed in the economic analyses. Reductions in uptake

will reduce the net cost savings of a real-world genetic testing service. Actual compliance with surveillance programs will also fall short of the 100 percent level assumed in economic analyses. It is possible, however, that compliance with the surveillance program will be higher among family members who test positive for the FAP genetic mutation than for relatives who are not offered the test, reject it, or for whom a test is inconclusive. This impact of a true-positive genetic test result may raise the chances of early polyp detection, which might lead to a longer delay in the onset of cancer.

4.2 Hereditary Nonpolyposis Colorectal Cancer (HNPCC)

The preceding discussion of familial adenomatous polyposis (FAP) illustrated a case where the value of the testing service came from the reduction in the need for clinical surveillance among populations at high risk of a hereditary disease. Analogous health care cost savings may arise from genetic testing for families with a history of hereditary nonpolyposis colorectal cancer (HNPCC). The case of HNPCC is more complicated, however; illustrating some of the many aspects of genetic testing programs that must be considered.

HNPCC is a rare Mendelian disorder that is associated with an 80 to 90 percent risk of cancer. In comparison with FAP, which is a single-gene, "full penetrance" disorder, multiple genes lead to inheritance of HNPCC, thereby reducing the sensitivity of common genetic tests (Rabelo, Foulkes et al. 2001). This would tend to render genetic testing for HNPCC families less favourable than was the case with FAP families. However, those with HNPCC are at significantly higher lifetime risk of many forms of cancer, each of which may require a separate surveillance program.

In addition to an 80-90 percent lifetime risk of colorectal cancer, HNPCC is associated with a 43 to 60 percent lifetime risk of endometrial cancer, a 13 to 19 percent lifetime risk of gastric cancer, a 9 to 12 percent risk of ovarian cancer, and elevated risks of several other forms of cancer (Burt 2000). Consequently, in addition to colonoscopy, recommended surveillance protocols for HNPCC patients include pelvic exams, transvaginal ultrasonography, upper gastrointestinal endoscopy and urinalysis every 1 to 2 years starting at age 30-35 (Burt 2000). Although one study showed that regular colonoscopic surveillance was cost effective for males

with HNPCC (Vasen, van Ballegooijen et al. 1998), no known studies have assessed the cost-effectiveness of such a screening protocol. Notwithstanding this fact, a genetic testing program analogous to the FAP program described above could avoid the costs (and inconvenience) of these multiple surveillance protocols for detected true-negatives. This saving might be sufficient to justify the cost of such an elaborate screening program. There is insufficient data to estimate the magnitude of costs impact for the province of Ontario.

Although there may be net benefits (savings) from genetic testing services targeted at families with a history of HNPCC, population screening for the disease is unlikely to be cost effective at present. One study that assessed the costs and benefits of population screening for HNPCC indicates that such a program would only be cost-effective—relative to other established cancer screening programs—if extremely favourable assumptions are made (Brown and Kessler 1996). Specifically, screening for HNPCC showed the promise of cost effectiveness only when it was assumed that surveillance and preventative treatments are 100 percent effective at preventing colorectal cancer, that genetic tests have 100 percent sensitivity and specificity, that tests are supplied at cost (i.e., without markups associated with patents), and that the prevalence of HNPCC was in the order of 1 in 100 to 500 individuals. None of these assumptions is realistic on their own; they are almost certainly not valid when combined. This study served to indicate that caution should be taken when considering population screening for a genetic condition that could be targeted—in this case, based on family history (Brown and Kessler 1996).

4.3 Hereditary Hemochromatosis

The preceding examples—familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC)—illustrated cases of where genetic testing services was best targeted at families at risk of serious illnesses. In the absence of genetic testing in both cases, all members of at risk families would be subject to ongoing clinical surveillance in an attempt to detect disease progression early. Under these special circumstances, genetic testing had the capacity to *reduce* the use of health care services by identifying true-negatives: individuals who would have otherwise been thought of as "at risk." Genetic testing services in many other circumstances have the capacity—indeed, the intent—to induce the use of more

surveillance and preventative health care services. One such example is testing for hereditary hemochromatosis.

Hereditary hemochromatosis is one of the most common Mendelian disorders, particularly among people of northern European descent. One in ten people of northern European descent carry a recessive hereditary hemochromatosis genetic mutation. When two of these are inherited, one from each parent, an individual has at 60 to 90 percent chance of developing pernicious levels of iron saturation in bodily tissues—especially the liver, heart, and joints. Iron levels increase gradually between the ages of 20 to 60, along with signs and symptoms such as fatigue and joint pain years; and, if left untreated, iron saturation results in hepatica cirrhosis, diabetes, or heart disease. Treatment, involving phlebotomy (bloodletting) on a regular basis, is safe and effective, resulting in normal life expectancy and quality of life if started before serious organ damage (Burke, Thomson et al. 1998)

Because of its high prevalence, and because of the non-specific nature of early signs and symptoms, hereditary hemochromatosis appears to be an excellent candidate for population screening among people of northern European descent. Because preventive treatment costs are relatively low, screening and surveillance costs are the primary cost considerations in an analysis of such a program. There are (at least) two alternative approaches to screening for hereditary hemochromatosis: clinical screening followed by genetic confirmation, or genetic screening followed by clinical surveillance (Adams and Valberg 1999).

If clinical screening is conducted, people with blood iron saturation above a threshold will be given counseling and a genetic test to determine if hereditary hemochromatosis is the cause of iron saturation. Patients with high iron saturation may also be given other diagnostic tests to determine alternative causes of the elevated iron levels. Thus, positive results of clinical screening trigger test costs, followed by treatment for confirmed hereditary hemochromatosis diagnoses.

If screening is conducted using a genetic test, those who test positive for the pair of hereditary hemochromatosis genetic mutations will be placed on a program of clinical surveillance to determine when treatment will be necessary. Positive genetic test results trigger

surveillance costs, followed by treatment for those whose iron saturation levels exceed an acceptable threshold. Because of the imperfect predictive power of the hereditary hemochromatosis genotype, between 10 to 40 percent of those with positive test results will never show signs of hemochromatosis.

Adams and colleagues used decision modeling for a hypothetical population of blood donors to compare the costs and benefits of clinical versus genetic screening for hereditary hemochromatosis (Adams and Valberg 1999). Their results indicated that clinical screening followed by genetic testing was more cost-effective than genetic screening followed by surveillance. This was because the cost of genetic testing was sufficiently high that it was better applied to those in a focused population. It would take a reduction in genetic testing costs from US$178 to US$28 to alter the finding (Adams and Valberg 1999). The incremental, net present value of savings generated per blood donor screened by the clinical test followed by genetic testing of at risk persons was US$1 in the Adams and Valberg study (Adams and Valberg 1999). The incremental cost of genetic screening was US$200 per person. If a quarter of Ontario's 800,000 residents between ages 25 and 19 were screened by clinical test followed by genetic testing only for those with elevated iron levels, and the Adams and Valberg result is assumed a reasonable estimate for this population, the cost savings from such a program for the province of Ontario would be of the order of $300,000 (Canadian). The cost of a similar program using untargeted genetic screening would be in the order of $60,000,000.

Consistent with a hypothesis that, where possible, focused genetic testing will be more cost-effective than broad screening, genetic testing for family members of individuals with confirmed cases of hereditary hemochromatosis has been shown to be cost-effective (El Serag, Inadomi et al. 2000). This is because family members are at higher risk of the disease.

It is noteworthy that previous evaluations of hereditary hemochromatosis screening programs did not consider the possible benefits of having those at risk of hereditary hemochromatosis take part in routine blood donations. In May 2001, the Canadian Blood Agency announced that healthy hemochromatosis patients could donate blood every 56 days—a program that reduces the cost of treatment, while putting the otherwise-discarded blood to good use. This new possibility will increase the cost-effectiveness of a screening program for

hereditary hemochromatosis—though it would not likely change the relative cost-effectiveness of clinical over genetic screening.

4.4 Alzheimer's Disease

The final test that we consider, and the second test for which we present original costs estimates, is a risk factor test (APOE) for Alzheimer's Disease (AD). The genetic test may generate cost savings to the extent that it can target use of effective preventive therapy that delays onset of AD. It can generate increased costs from the test itself and from unnecessary use of preventive care among false positives. Our results must be seen as highly tentative given the quality of the underlying data upon which we based the study.

AD is a progressive neurodegenerative disorder with clinical symptoms of impairment in memory and language in early stages, progressing to loss of autonomy for self-care and need for full-time supervision in later stages. Between 6 and 8% of persons over the age of 65 have AD with the prevalence increasing to around 30% for persons over 85 years of age. Despite this high prevalence and significant impact on patient autonomy and quality of life, no cure exists for AD. Recently developed drugs such as Donepezil hydrochloride (Aricept) have been shown to be effective in delaying the onset of AD and in delaying disease progression in patients with confirmed AD.

A small percentage (about 5%) of AD is inherited in autosomal dominant fashion. In the case of familial AD, onset is generally early. The vast majority of AD is sporadic. AD that is sporadic generally occurs later in life and is genetically complex. It is likely that several genes and many environmental influences contribute to the risk of developing the disease. Only one gene has been confirmed as a risk factor for late onset AD: APOE (Blacker 2000).

APOE represents a risk factor genetic test. It is one of the more complex genetic tests that could be integrated into clinical practice. Although it has been marketed in the US for diagnostic purposes, its use in clinical practice has been controversial. The consensus in the clinical literature is that, at present, APOE testing is not appropriate for clinical use. This judgement is based primarily on the poor sensitivity and specificity of the test in identifying AD,

particularly compared to clinical diagnosis (Mayeux et al. 1998). APOE is not currently used predictively, though original expectations were that it would serve predictive purposes. It is argued by some that APOE genotyping may contribute to the early detection of late-onset AD because it appears to predict conversion to full AD among patients with mild cognitive impairment. But again, there is no consensus on its use in this context (Blacker 2000).

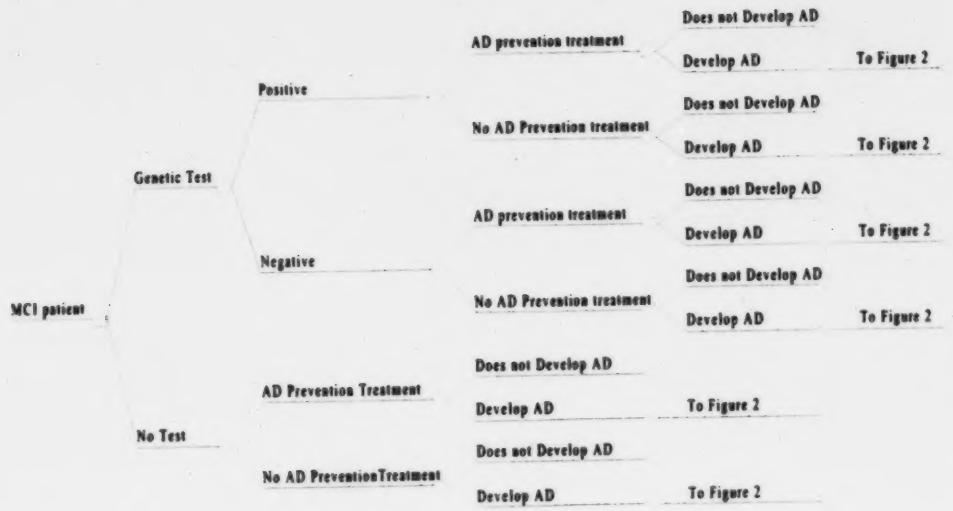
4.4.1 Costing Analysis

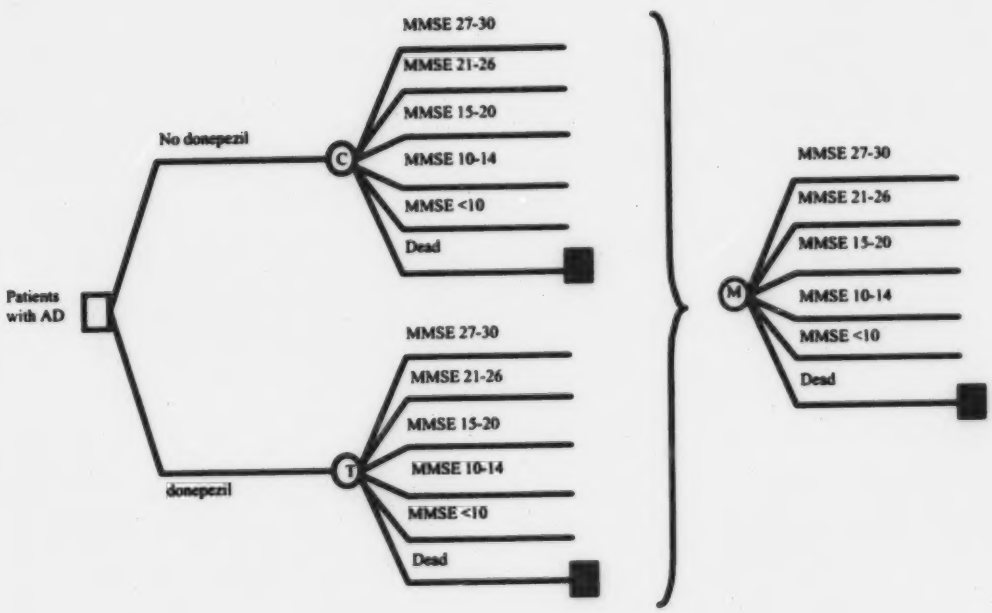
The costing model assesses the cost impact of a relatively conservative testing program targeted at a high-risk population: those already diagnosed with mild cognitive impairment (MCI). The model compares the costs of two strategies for testing and treating patients with MCI.

The testing strategies of the analysis are depicted in Figure 4. The conventional arm (no genetic test offered) is depicted in the lower half or the diagram. Patients diagnosed with MCI are offered a currently available preventive treatment (Denepezil): 20% of such patients are assumed to take-up the preventive treatment and preventive treatment is assumed to delay onset of AD by 6 months. It is assumed that 50% of MCI patients will eventually convert to AD. Individuals who convert to AD progress through more severe stages of the disease following a pattern documented in a previous study of AD (O'Brien, Goeree et al. 1999). We assume that 50% of those who convert to AD will pursue active AD treatment (again, the drug Denepezi) to slow progression of the disease (this treatment is in addition to the range of services, including those of health providers, caregivers, community programs and long-term care facilities used by all AD patients as their disease progresses).

For the APOE genetic test strategy, we assume that: the test costs $500; that 100% of those diagnosed with MCI take-up the genetic test; and that 40% of the test results are positive. We further assume that all of those with a positive test result take-up preventive treatment, and 50% of such individuals convert to AD (though preventive treatment delayed onset 6 months just as in the base case). Among those with a negative test result, we assume that 0% take-up preventive treatment, and that 20% convert to AD. We assume that all those who convert to AD behave identically to individuals in the conventional arm.

Figure 4: Decision Tree for APOE Costing Model





The model considers all costs that arise during an 8 year period following diagnosis of MCI. Costs are discounted at a rate of 3% and expressed in Cdn 2001 dollars.

The key difference between the two strategies, especially with respect to health care costs, arise from: (1) the costs of the test in the genetic test strategy; (2) a slightly higher rate of take-up for preventive treatment in the genetic test arm (all 40% of those who test positive vs 20% of all MCI patients in the absence of the test); and (3) savings associated with delayed onset from uptake of the preventive treatment. See Appendix C for a full description of the costing model.

4.4.2 Costing Results.

The expected cost of conventional treatment over an eight-year period of follow-up of individuals diagnosed with MCI is estimated to be $24,245 per patient. The expected cost of the APOE genetic test strategy for patients diagnosed with MCI over the same eight year period are estimated to be $24,824 per patient. Therefore, among those already diagnosed with MCI, a genetic testing program is estimated to increase health care costs by $579 per patient.

The Alzheimer Society of Canada reports that 83,200 elderly Canadians are expected to develop dementia in 2001. Alzheimer's disease accounts for approximately 40 percent of such dementias, and Ontario represents 38 percent of the national population; therefore, approximately 32,000 cases of Alzheimer's disease may be expected in Ontario. If we assume that the population displaying MCI (some of which will develop AD, some of which will not) is on approximately the same order of magnitude (approximately 1 in 10 persons aged 60 to 65), the incremental cost impact of this hypothetical screening and treatment program would be in the ballpark of $10 to $20 million for the province of Ontario. This scenario is strictly hypothetical, and in no way should be generalized to the broader population. If a testing program were applied to the broad population of Ontario residents aged 60 to 64, not only would the scale of the testing program increase 10-fold, the incremental costs generated by the testing service would likely change due to differences in base-line risk status and likely conversion rates from APO-e status to Alzheimer's Disease.

Sensitivity Analysis. The lack of validated estimates for a number of model parameters meant that we had to rely on "educated guesses" from experts in the field to derive the above cost

estimates. We therefore carried out a series of sensitivity analyses on these model parameters. The relative cost results were fairly insensitive to alternative assumptions for the following model parameters: the mean number of months before MCI progresses to AD for untreated patients; the probability of developing AD in patients with a negative mutation test result; the probability of seeking treatment for AD; and the cost of active treatment for AD (with or without active AD treatment). The results of varying values for six other key model parameters demonstrate that the relative cost findings are sensitive to a number of important model variables. These variables include: the cost of the test, the prevalence of the genetic mutation among those with MCI , the assumed effectiveness of preventive treatment in delaying onset of AD, the assumed proportion of individuals with a positive test who take-up preventive therapy, the assumed proportion of individuals with a negative test result who take up preventive treatment, the probability a person who does not get the test will take-up preventive treatment, and finally, the probability that a person with a positive genetic test result will develop AD. Details regarding the sensitivity analysis can be found in Appendix C. The bottom line is that there is a great deal of imprecision in our cost estimate.

4.5 Costing Summary

Any discussion of the cost impact of predictive genetic testing that strives to be based on a good evidence is biased toward full penetrance and predisposition tests and away from risk factor tests. This is because past genetic testing has been focused on full penetrance tests for rare, sing-gene disease, hence, these are two contexts for which good test, disease, epidemiologic and cost data exist. Among risk factor tests, the most feasible scenarios to cost tend to be more conservative applications of the test (e.g., in our APOE study, we modeled a targeted screening program for patients already diagnosed with MCI). The situations that will likely generate the largest cost effects are those which are most difficulty to model at this time.

5.0 The Bigger Picture

As illustrated in the preceding sections, estimating the economic impact of genetic testing services is far from straightforward. Part of the complexity stems from the complicated and

inexact relationship between genetics and health (Evans, Skrzynia et al. 2001). Further challenges come from uncertainty regarding how genetic information will influence patients, providers, and other stakeholders. Neither the simplified micro-assessments of individual tests previously conducted in the economic literature, nor the grand promises of enthusiastic promoters of genetic technology address many of the important issues at stake. A balanced assessment of genetic testing services must consider not only the technology, but also that there are important, albeit difficult to quantify, psychological costs associated with genetic testing; that individuals will, upon testing positive for a gene-related risk, seek to reduce their susceptibility, regardless of whether appropriate health care is available; that the genetic testing industry is—now more than ever—profit driven; and that it is difficult to evaluate the long-term impacts of preventative treatments for gene-related risks. Finally, from the perspective of the public provider of health care, coverage decisions must be considered with emphasis on both access and appropriateness of use.

Imperfections in test sensitivity and test specificity lead to false negatives and false positives that must be accounted for in any screening or diagnostic service. In the case of genetic testing, however, the complex and inexact relationship between genetics and health, as well as the potentially long period between genetic testing and illness onset, exacerbate these issues. Pre-symptomatic genetic tests that predict illness with certainty are rare. Most nascent genetic tests aim to identify populations *at risk* of illness. Some people with genetic susceptibility will not develop the illness of concern, while some "normal" genotypes will. As discussed above, the costs and consequences of these dynamics must be considered.

A primary purpose of predictive genetic testing is to alter the behaviour of persons identified at risk of future illness. Knowledge of a genetic susceptibility to illness focuses attention and intention on prevention. Patients and practitioners may be prone to action for fear of the regret (or legal liability) that might ensue should nothing be done. The impulse to respond may, in some cases, exceed evidence of preventative or treatment effectiveness. However, it is also possible that patients labeled at risk of illness will experience a sense of fatalism, possibly reducing (or at least not encouraging) preventative behaviours (Marteau and Lerman 2001). These dynamics are not new, however. They are similar to the impacts from non-genetic

screening programs. The response of individuals to information about health risk depends on the test, context, and perceived efficacy of preventative behaviours (Marteau and Lerman 2001).

In addition to induced preventative behaviours (or lack thereof), susceptibility information can also have an impact on health status. Direct health impacts of health risk information have been observed in non-genetic screening programs (Peckham and Dezateux 1998) (Stewart-Brown and Farmer 1997). In some settings, those identified at risk of certain illnesses through non-genetic screening programs (e.g., hypertension and cholesterol screening) have been shown to have lower self-reported health status and/or higher all-cause morbidity and mortality (Peckham and Dezateux 1998) (Stewart-Brown and Farmer 1997). This form of self-fulfilling prophecy when labeling populations at risk of future ill health may carry over to genetic screening if patients interpret risk information in a similar manner. Though difficult to predict, these dynamics must be weighted against the benefits to those who ultimately gain from screening and subsequent treatment.

One determinant of behavioural and health responses will be how the benefits and costs of testing, and ultimately of treatments, are communicated to the public, and to practitioners. Unlike most non-genetic screening services, for-profit corporations now hold exclusive patents on the many genetic testing technologies. This affects not only the cost of the tests themselves, but also the way that genetic testing is portrayed to providers, patients, and the general public. Patents concentrate the economic interests associated with specific technologies by conferring a temporary monopoly upon the inventor. The reward for invention is determined by the price the market will bear for the technology, and the extent of its adoption, giving an economic incentive to push for rapid and broad application of new, patented technologies. As the breadth of genetic testing services expands to include the promotion of tests for common disorders, the potential demand induced by marketing may outpace our capacity to offer genetic counseling necessary for informed consent (Collins 1999). Moreover, some genetic testing services may be marketed before effective preventative treatments are available. Some tests may even be promoted before much can be done to manage the risks they identify.

Where preventative therapies currently exist, genetic testing services may also be promoted by those selling these goods and service that could be seen as complementary to the

genetic test. This has occurred in the case of non-genetic screening programs—e.g., bone-densitometry, serum lipid testing—where specific companies selling drugs to manage those risk factors have financial interest in promoting the screening programs themselves. Current models of pharmacological disease management may evolve along with genetic testing, offering products and services to the "market segment" created by those determined to be at greater than standard risk of given illnesses. In many cases, the cost of complementary treatments will exceed (possibly by far) the cost of the genetic testing itself.

The evaluation of preventative responses to genetic testing services (including pharmacological disease management responses) is critical for determining the overall cost of genetic testing service. This task will not be easy. Clinical benefits from preventative products and services consumed upon the identification of genetic susceptibility to many illnesses will not be observable for many years, in some case decades. As the time-line involved becomes longer, the savings or health improvements required to justify ongoing costs of prevention must increase. Determining the end-state savings from prevention will be difficult because it is uncertain whether what is known about the expected benefits of existing treatment modalities can be applied to treatments given to those at genetic risk of illnesses. For example, treatments used to manage biological factors associated with the risk of later illness—such as blood pressure or cholesterol levels—have historically been approved based on changes in the biological marker as a surrogate of their impact on long-term health. It is yet unknown whether such surrogates will apply to risks of a genetic origin. The costs of treating susceptible populations with such therapies will, nevertheless, add up over time as we wait for evidence of long-term efficacy.

The importance of the treatment or preventative therapy that follows genetic testing services highlights a consideration regarding the funding of genetic testing services themselves. The costs of genetic testing itself may be outweighed by the costs related to services induced by the test results. Consequently, whether or not a test is provided publicly, much of the cost associated with goods and services complementary to the test will be born by the public system.

Coverage decisions will of course have to be made on a case-by-case basis. One can envision three scenarios for the coverage of a given predictive genetic test: (1) no public coverage; (2) unrestricted public coverage, or (3) criteria-based public coverage. In all cases, the

publicly financed health care system (so long as it remains reasonably comprehensive) will end up paying for many services complementary to the genetic test, including pre- and post- test primary care, induced medical or surgical treatments, or long-term preventative therapy (possibly including drug costs, depending on eligibility). Caulfield and colleagues offer a number of criteria to determine whether the tests themselves are appropriate for public funding: these include whether the test is morally appropriate, safe, accurate, and clinically useful (Caulfield, Burgess et al. 2001). When tests are available exclusively through the private sector, willingness and ability to pay for tests becomes the mechanism of test rationing. This allocation method may not be consistent with allocation according to need. In cases where the test could be deemed medically necessary, but the patient is unable to afford the test, this will violate the spirit of the Canada Health Act. Of course, when a test is immoral, unsafe, inaccurate, or clinically useless, private payment for tests does not violate principals of Canada's health care system. Private payment for such dubious tests may still cost the public system in terms of complementary services. In general, leaving predictive genetic testing services to the private sector will save the publicly funded system the cost of the tests themselves, but if forsakes the ability to regulate use.

Unrestricted access to tests through the public system will alleviate financial barriers to access, but may result in excessive test use. Many tests currently available prove to be most appropriate and cost-effective when applied to limited populations—e.g., those with a familial susceptibility to a given illness. If demand for tests induced by promotion of the testing technologies extends beyond the realm of targeted populations, costs will increase without necessarily being accompanied by commensurate savings or health improvements.

Consequently, the wisest policy in many circumstances may be to provide public coverage for the test along with test service programs that target delivery at high-risk populations. That is, public coverage may give public funders the most levers to limit use to situations where the tests are most likely to product benefits and to avoid broad, inappropriate uptake that would generate large costs to the public system. Criteria-based public coverage for many genetic tests may ensure access and efficiency. Unnecessary use of tests will only be avoided, however, if denial of public coverage on reasoned and needs-based grounds sends a

signal to patients that dissuades them from seeking the test through the private market—complementary costs of which would ultimately be borne by the public system.

6.0 Conclusions

The above analyses highlight the difficulties encountered in predicting the cost impacts of predictive genetic tests on health care costs. As with most health care services, no general a priori statements can be made regarding the cost impact. The effect of each test depends on the specific features of the test, how it is used, and the current practice with respect to the condition associated with the genetic test. Further, even a "good test" that has the potential to be cost reducing when targeted at high-risk populations could generate large increases in costs if applied more widely. Many other tests will unquestionably be cost increasing (and may also generate corresponding gains in health and well-being if wisely used). A couple of key points emerge from this analysis.

Full penetrance tests, which test for rate diseases and can be well-targeted, will have the smallest impact on health care costs. Predisposition tests, if well-targeted will also likely have small costs impact. However, because the test for specific heritable forms of more common diseases, there is some possibility that they may be applied more broadly than in appropriate, generating large cost impacts. Risk factor tests will likely have the largest impact on costs, and they pose the greatest challenge for limiting use to appropriate conditions.

The cost impact of predictive genetic testing itself is only one component of overall system costs. In many cases, it is a minor cost compared to cost for surveillance, prevention or treatment. Hence, although it is appropriate to ensure that the tests can be delivered at the lowest cost possible, attention also needs to be focused on other cost effects of introducing a predictive genetic test service. Hence, even if the test is offered only privately, much of the cost impact may arise in the publicly financed components of the system. Coverage policies need to take into account the overall relation between where the costs arise and the ability of the public funder to control access to tests that generate public-sector costs even when the test is privately financed.

Finally, a number of key parameters that influence the impact of predictive genetic tests on overall system costs are under the control of health system decision makers at various levels of the system (e.g., the design of the testing service and how well the test is targeted). Hence, the impact of predictive genetic tests is not an immutable force. Wise policy choices can ensure that savings are realized were possible and, where cost increasing under all circumstance to ensure that the most value is obtained for the resources devoted to testing.

Appendix A

A Fully Penetrant Predictive Genetic Test: Familial adenomatous polyposis (FAP).

1. Nature of Genetic Test/Syndrome

a) *Predictive Power of the Test:* Familial adenomatous polyposis (FAP) is a rare, hereditary, colon cancer predisposition syndrome. FAP is inherited in an autosomal dominant manner; thus first-degree relatives of FAP-affected individuals are at a 50% risk of inheriting the mutation. FAP exhibits 100% penetrance, assuming FAP-affected individuals do not die prematurely. That is, individuals who inherit the mutation for FAP will develop multiple polyps and have approximately a 100% risk of colorectal cancer by the age of 50. FAP is caused by mutations in the APC gene, which is a tumour suppressor. Thus mutations in this gene "shut off" the tumour suppressor function, leading to development of polyps. There have been more than 300 different mutations reported in the APC gene.

Tests for FAP with the highest sensitivity, at approximately 90%, involve full gene sequence or linkage analysis. However, these approaches are expensive and technologically demanding. Thus, many laboratories do not conduct them. A common alternative is to use the protein truncation test. This test is easier and cheaper to perform than full gene sequencing. It has a sensitivity of approximately 70-80% in detecting mutations.

In summary, this is a fairly straightforward predictive genetic test both in theory and in practice. The major limitation in clinical validity derives from the use of a testing protocol with less than 100% sensitivity.

b) *Nature of the Clinical Condition:* The estimated incidence of FAP is approximately 1 in 8300 to 1 in 14,025 live births. The syndrome affects both sexes equally and has worldwide distribution. FAP is clinically manifested by hundreds of adenomas throughout the colon; approximately 15% of patients have polyps by age 10, 75% by

age 20, and 90% by age 30. If left untreated there is almost 100% probability that one or more polyp will progress to malignancy.

FAP is a heterogeneous disease. Beyond the development of multiple polyps in the colon, extracolonic manifestations are common in FAP patients. These extracolonic features include polyps, cutaneous lesions, desmoid tumours, osteomas, thyroid cancer, brain cancer and more.

2. Nature of Genetic Test Service

a) *Case Finding:* Screening for persons at risk of FAP is targeted at family members of an identified proband. Genetic testing begins with the proband to detect the specific mutation involved and to determine whether the mutation in that family can be identified by the test that is being used.

b) *Surveillance:* Individuals at risk for FAP undergo regular surveillance. This involves colonic examinations by flexible sigmoidoscopy or colonoscopy beginning at a young age (≈10 years). Depending on the age of the patient, most physicians will recommend annual or biannual surveillance intervals.

The proband is a presumptive mutation carrier and her/his first-degree biological relatives are assumed to be at 50% risk. Predictive genetic testing can discriminate between family members who are at 100% risk and those who did not inherit the mutation, and who therefore are at 0% risk of FAP. Where no mutation can be identified in the proband (because of reduced sensitivity of the test), testing in family members will not be conclusive. They remain at 50% risk and continue to be candidates for clinical surveillance.

Because of the heterogeneity of this genetic disease, at-risk individuals are generally counselled regarding their risk of other conditions such as Desmoid tumours. Multiple screening and preventive strategies are needed to manage the risks of these auxiliary diseases (Burt 2000).

c) *Prevention:* Preventive strategies usually entail removal of polyps from the colon, if the polyps are in the early stages of development. These procedures are used primarily to preserve quality of life and tend to only delay FAP onset. The most common form of treatment for FAP patients is colectomy. This surgical procedure is usually performed when the number of polyps is too high to control by polypectomy and the subsequent cancer risk is also very high.

A Predisposition Predictive Genetic Test: Hereditary nonpolyposis colorectal cancer (HNPCC)

1. Nature of Genetic Test/Syndrome

a) *Predictive Power of the Test:* Hereditary nonpolyposis colorectal cancer (HNPCC) is a rare, hereditary, colorectal cancer (CRC) predisposition syndrome. This syndrome is transmitted in an autosomal dominant manner (Rabelo, Foulkes et al. 2001). An estimated 80-90% of individuals with HNPCC will develop colorectal cancer (Hahn, Saeger et al. 1999).

The high predictive power of HNPCC testing in theory is generally not realized in practice. HNPCC is caused by mutations in several mismatch repair (MMR) genes (Rabelo, Foulkes et al. 2001). Mutations in the two most common such genes (*hMSH2* and *hMLH1*) account for 95% of all HNPCC mutations (Giardiello, Brensinger et al. 2001). Despite the high frequency of common mutations in the *hMLH1* and *hMSH2* genes among HNPCC patients, the predictive power of HNPCC genetic testing is debatable. While the analytic sensitivity for finding mutations in these genes may be very high, the rate of false-negatives is also high with the involvement of multiple, often untested, genes. Thus, negative test results for the two most common genes are interpreted as inconclusive. By comparison with FAP, the multiple genes that lead to HNPCC increase the frequency of false-negatives (Rabelo, Foulkes et al. 2001).

b) *Nature of the Clinical Condition:* HNPCC represents 2% to 4% of all colorectal cancer cases. Patients with HNPCC develop CRC at an average age of 44 years in the right side of the colon, proximal to the splenic flexure. This is contrast to sporadic CRC,

which has a typical onset of approximately 64 years and develops in the left side of the colon (Petersen, Brensinger et al. 1999).

2. Nature of Genetic Test Service

a) *Case Finding:* Unlike FAP which has a characteristic clinical hallmark (specifically, polyps in the colon), HNPCC lacks any obvious clinical hallmark in the colon. This makes it difficult to definitively identify the proband. Detection of HNPCC relies on an accurate family history and detection of clinical hallmarks clinical hallmarks in other regions of the body, including the endometrium, ovary, renal pelvis, ureter, small bowel, and stomach (Rabelo, Foulkes et al. 2001).

Due to the complex and often undetectable phenotype of HNPCC, the Amsterdam and Bethesda diagnostic criteria were developed to aid physicians to identify HNPCC-affected individuals (Giardiello, Brensinger et al. 2001). These criteria identify characteristics in an individual's family history that render them at high risk. However, these criteria differ markedly in the family history data that they consider relevant. The first and most restrictive criteria – the Amsterdam criteria I – include relatives with colorectal cancer. The Amsterdam criteria II accept relatives with various HNPCC-associated cancers (colorectal cancer, cancer of the endometrium, small bowel, ureter, or renal pelvis) (Giardiello, Brensinger et al. 2001). These varying selection criteria reflect the heterogeneity of this disease and the fact that knowledge about this disease is changing.

b) *Surveillance:* Regular colonoscopic surveillance is recommended for individuals with HNPCC to begin between the ages of 20 and 30 and performed at regular intervals of 1-2 years. Once the patient reaches the age of 40 colonoscopic surveillance is recommended every year (Hahn, Saeger et al. 1999).

Like FAP, genetic testing begins with a proband to confirm mutation-positive status and to determine the inherited MMR gene mutation. Since sensitivity of the most commonly used genetic tests are reduced, a high proportion of tests are inconclusive and clinical surveillance for these individuals should continue.

Because of the heterogeneity of this genetic disease, at-risk individuals are generally counselled regarding their risk of other conditions, such as endometrial cancer in women. It is also often recommended that women pursue different preventive and treatment options, notably ovario-hysterectomies. Systematic screening and preventive strategies are needed to manage the risks of these auxiliary diseases. (Burt 2000)

Patient behaviour has been well documented for HNPCC. It is often hypothesized that, given the invasive nature of colonoscopic surveillance, uptake rates of genetic testing and colonoscopic surveillance for HNPCC would both increase if genetic testing could provide the patient with information of their risk (i.e. positive vs. negative mutation status). In a study by Stanley et al., the uptake of colonoscopic surveillance is only 77%, and although the uptake of genetic testing was only slightly higher than that of surveillance, at 81%, those mutation-negative individuals could be removed from the invasive surveillance screening programs (Stanley, Gaff et al. 2000). Interestingly, another study conducted by Lerman et al. found much lower rates of uptake for predictive genetic testing for HNPCC, at 43%. Uptake is influenced by several factors, including education levels, marital status, previous participation in a genetic study, and the presence of depressive symptoms. Thus, patient behaviour with regards to uptake can be unpredictable and volatile. (Lerman, Hughes et al. 1999)

c) *Prevention:* Endoscopic surveillance combined with polypectomy greatly reduces the incidence of CRC in at-risk HNPCC persons. When a carcinoma is manifest in a carrier subtotal colectomy with ileorectostomy is strongly recommended, especially for young adults who are likely to benefit most from this intervention (Hahn, Saeger et al. 1999).

The clinical manifestation of HNPCC in the many tissues other than the colon requires complex clinical management with tissue-specific treatments. If the clinical manifestation of HNPCC is undetected with surveillance and metastasizes into cancer, prevention is no longer an option and treatments will then take the form of disease control.

A Predisposition Predictive Genetic Test: Hereditary hemochromatosis (HH)

1. Nature of Genetic Test/Syndrome

a) *Predictive Power:* Hereditary hemochromatosis (HH) is one of the most common autosomal recessive disorders in Western populations, with homozygote frequencies of 2-5 in 1000 in the general population (Stuhrmann, Graf et al. 2000). It is particularly prevalent among individuals of northern European descent, with a prevalence of 1 in 200-300 (Lyon and Frank 2001).

HH is a Mendelian disorder of iron overload. As a recessive condition, HH can be manifested when an individual has two copies of the gene (i.e., is a homozygote). HH is inherited if two carriers reproduce; the probability of two carriers producing an HH-affected child is 25%. This probability increases if one of the parents has the disorder (i.e., is a homozygote).

Although there have been 37 allelic variants reported, HH is caused primarily by one of two mutations in the HFE gene, C282Y and H63D (Hanson, Imperatore et al. 2001). The H63D mutation however, appears to have little effect when inherited alone, but may contribute to HH when inherited with the C282Y mutation, producing the compound heterozygous genotype (Lyon and Frank 2001).

HH has been estimated to have a penetrance for iron overload ranging from 75% to 96%, and for other symptoms is approximately 50%. Penetrance in HH is influenced by many factors, including the type of HFE mutation, age, sex, environmental influences, diet, and extent of iron loss throughout the individual's life (Lyon and Frank 2001). Men tend to exhibit symptoms of HH to a much larger degree than women. This is due to the excessive loss of iron throughout a woman's life due to menstruation, pregnancy, lactation, and lower iron intake relative to need. (Hanson, Imperatore et al. 2001)

Tests can detect the most common genetic mutations related to HH over 99 percent of the time. Despite the high analytic sensitivity of HH genotyping the predictive power

is much lower owing to the incomplete penetrance of the HH genotype. Consequently, mutation detection cannot predict disease severity or age of onset.

b) *Nature of the Clinical Condition:* Hemochromatosis is characterized by excessive absorption of iron in the liver, skin, heart, joints, and other tissues. Iron levels build up in these areas over decades, resulting in a gradual onset of non-specific signs and symptoms, such as fatigue and joint pain, between 20 to 60 years of age. Untreated hemochromatosis results in hepatica cirrhosis, diabetes, or heart disease (Hanson, Imperatore et al. 2001). Survival rates are generally lower in symptomatic HH patients, with cirrhosis being the primary factor affecting survival. The mortality rate in North America is 1.8; this rate is far lower than the prevalence of the gene, indicating low penetrance and/or underdiagnosis. (Hanson, Imperatore et al. 2001)

2. Genetic Testing Service: The Health System Context

a) *Case Finding:* Because of its high prevalence and because of the non-specific nature of the signs and symptoms, hereditary hemochromatosis could be a candidate for population screening, though many recommend against it (Lyon and Frank 2001).

If population screening is done by the genetic test, the screening identifies those who are susceptible to hemochromatosis. Alternatively, non-genetic screening can be conducted by blood tests to assess iron saturation levels (2000). If clinical screening is conducted first, those with iron saturation above a threshold will then be given the genetic test to determine if hereditary hemochromatosis is the cause of iron saturation. Patients with high iron saturation may also be given other diagnostic tests to determine alternative causes of the elevated iron levels. If genetic testing is conducted first, those with a genetic susceptibility for hemochromatosis will be placed on a program of clinical surveillance to determine if treatment will be necessary. Those who show signs of elevated iron saturation will then be placed on preventative treatment.

b) *Screening:* Individuals identified as being at risk of developing HH would have to be enrolled in some sort of screening program to monitor individuals for early signs of the

disease, and decide which individuals need preventative treatment. A large percentage (between 10 and 40 percent) of people with the high-risk genetic mutations do not develop the clinical disease of hemochromatosis. Many individuals will therefore have to be monitored who are not, ultimately, at risk. In addition, there will be challenges associated with maintaining contact with at-risk individuals, and ensuring their participation.

c) *Prevention:* The preventative treatment of hemochromatosis is relatively benign and effective. It does not, however, come without costs; nor does its simplicity ensure perfect compliance problems. Preventative treatment involves phlebotomy (bloodletting) on a regular basis—between monthly and semi-annually. If HH is detected before expression of later, more serious symptoms, phlebotomy is an effective treatment, which will delay onset of HH. If HH is detected before any clinical manifestations (other than increased TS and SF levels), phlebotomy is used as a preventive measure. (Hanson, Imperatore et al. 2001)

Appendix B: Cost comparison of genetic testing versus clinical screening for familial adenomatous polyposis

This analysis is an extension and update of a previously published cost comparison of predictive genetic testing versus conventional clinical screening for familial adenomatous polyposis (FAP) conducted by Bapat and colleagues in 1999 (Bapat, Noorani et al. 1999). In this study we compare the costs of a strategy of predictive DNA testing versus conventional clinical screening for individuals with a family history of FAP. The starting point for the model is a patient presenting with clinically diagnosed FAP, whether that be through family tracing initiatives or through symptoms with subsequent clinical investigations. This cost analysis was conducted from the perspective of the Ontario Ministry of Health and all costs are expressed in CA 2001 dollars.

METHODS

A decision analytic model was developed to compare the cost of 2 general strategies for testing and screening patients with clinically diagnosed FAP and their immediate family members. Long-term screening and monitoring costs for patients with FAP (called the proband) are not included in this model as clinical screening would be considered the norm for this patient population. The model essentially compares the cost of screening immediate family members using conventional screening guidelines versus an alternative test and screen approach based on the outcomes of a genetic test on the proband and on family members.

Conventional clinical screening

The conventional screening approach for immediate family members of FAP patients involves frequent colonic examinations by either flexible sigmoidoscopy or colonoscopy repeated at regular time intervals. Guidelines for screening asymptomatic high risk FAP family members were established by an international consortium which recommended initiation of flexible sigmoidoscopy from age 10 onwards repeated every 2 years until the age 40 and every 3-5 years thereafter until age 60 (Bulow, Burn et al. 1993). For the present study we assumed that conventional clinical screening of first-degree relatives of patients with FAP would consist of a

baseline flexible sigmoidoscopy starting at age 10 with a repeat screen every 2 years to age 35, then every 4 years until age 50.

For both the clinical screening and genetics testing strategies, information about the first-degree relatives of FAP patients are required for costing purposes. More specifically, information is needed on the assumed number of first-degree family relatives and the age distribution of these relatives at the time the FAP patient first presents for clinical screening or genetic testing. Information for both of these variables was obtained from the Gastrointestinal Cancer Registry located at the Mount Sinai Hospital at the University of Toronto. From the database, based on 257 FAP registered families, the average number of first-degree relatives of FAP patients is 6. The proportion of first-degree relatives of FAP patients who are between the ages of 10 and 20 years is 60%, between the ages 20 and 30 years is 20%, and between the ages of 30 and 40 years is 20%.

Genetic testing and screening

The genetic test and screen algorithm assumed for this analysis uses an initial screening for the 2 most frequent mutations, at APC codons 1,061 to 1,053 and 1,309 to 1,311 by hetero-duplex analysis (HDA). If mutations are not detected by this screening, the APC gene is analyzed by protein truncation test (PTT) assay. For the PTT assay the entire coding region of the APC gene is divided into 6 overlapping segments and analyzed sequentially. The genetic testing algorithm is not 100% sensitive. For this analysis the sensitivity for the PTT assay was based on findings from the Mount Sinai Hospital. In this database of 124 FAP families screened by PTT analysis of the entire coding region of the ACP gene, gene mutations were identified in 92 families indicating 74% sensitivity for the PTT assay (92/124).

Under the genetic testing strategy we assumed all proband FAP patients would come in for initial genetic testing. If the test was found to be negative we assumed that first-degree family members would still come in for regular clinical screening due to the less than perfect sensitivity of the PTT assay. If the genetic test indicated a mutation in the proband, we assumed that all first-degree family members would come in for genetic counseling and testing. Since first-degree relatives of affected individuals have a 50% risk of inheriting the disease, one would

expect that the mutation would be identified in 50% of the first-degree family members tested. If a mutation was found in the family members, they would continue to be screened following the conventional clinical screening algorithm. If the mutation was not found in the first-degree family member then no further clinical screening is warranted. The genetic test need not be as extensive for the first-degree family member as it is for the proband. Instead, the testing focuses more specifically on the area of the gene where the mutation was found in the proband.

Decision analysis

We constructed a decision analytic model to compare the cost of conventional clinical screening versus genetic testing and screening for first-degree relatives of FAP patients. The overall structure of the decision tree is presented in Figure 1. The circles in the tree represent chance events that have associated probabilities of occurring. For example, for any given FAP family relative there is a probability that that relative would be between 10-20 years of age, a probability that they will be between 20-30 years of age and a probability that they will be between 30-40 years of age. In this model we assumed that all first degree FAP family members would have presented with clinical symptoms by the time they reached 40 years of age.

The genetic screening strategy is shown in the top portion of Figure 1. With this strategy the more complete genetic testing is done on the proband. If a mutation is found, all first-degree family members are invited to come in for genetic counseling and testing. In this model we have separated first-degree relatives into 3 age groups: ages 10-20, 20-30 and 30-40. Each of the first-degree relatives have a 50% chance of having the mutated gene and that is shown in Figure 1 with the branches labeled mutation found or mutation not found. If the mutation is found in the first-degree family member, then that family member is assumed to come in for regular clinical screening to detect polyps. If the mutation is not found in the first-degree family member then it assumed that the family member does not have a mutated gene and that no further clinical screening is warranted. The avoidance of clinical screening in first-degree family members where the mutation is not found is the primary advantage of the genetic testing strategy. This model essentially tests whether this reduction in screening costs more than offsets the initial up-front cost of genetic testing in the proband and in first-degree family members. Because the genetic test is not 100% sensitive it cannot be ruled out that family members are still at risk if the

tests in the proband shows to be negative. Therefore, under the genetic testing strategy where the mutation is not found in the proband, it is assumed that first degree family members would continue to come in for regular clinical screening.

The conventional clinical screening strategy is presented in the bottom half of Figure 1. With this strategy, all first-degree family members are assumed to come in for routine clinical screening. Depending on the age of the first-degree family member we assume that they are screened every 2 years up to 35 years of age, and every 4 years up to age 50. For example, a first-degree family member who enters the clinical screening program at age 10 would receive 17 examinations in total by the time they reach age 50.

Although the genetic mutation will only be found in 50% of first-degree family members (i.e., 50% are carriers), not all family members with the mutation will go on to develop polyps. Consistent with findings from other studies, we assume that only 90% of first degree family members with a gene mutation will go on to develop polyps (Prosser, Condie et al. 1994). Of the patients that go on to develop polyps, we assume that in 90% of the patients polyps will be detected at age 20, another 9% will be detected at age 30, and the remainder will be detected at age 40 (Bapat, Noorani et al. 1999).

Cost estimates for clinical screening and for genetic testing in the proband and first-degree family members were based on 1996 estimates from Bapat and updated to 2001 values using current reimbursement rates for genetic tests and current physician fee schedules.

The baseline probability and cost estimates used in the model are presented in Table 1. Shown in Table 1 is the sensitivity of the genetic test and finding the APC mutation in the proband, characteristics of the first degree family members, the risk of being an APC mutation carrier, the cost of the genetic test in the proband for first degree family members and the cost of clinical screening. All costs are expressed in 2001 CA dollars and the cost perspective of the analysis is that of the Ontario Ministry of Health.

Sensitivity analysis

The expected cost of each strategy can be determined by using base case or 'best estimates' for each model parameter. However, since the values for most model parameters are not known with certainty, it is common to test the impact of alternative values for these parameters. This is known as sensitivity analysis. For the present study, we conducted sensitivity analyses on the following key model parameters: test of the genetic test in the proband, test of the genetic test for first-degree family member, cost of clinical screening, the sensitivity of the genetic testing in the proband, and the number of first-degree family members.

RESULTS

Conventional clinical screening

The cost of each clinical screen using flexible sigmoidoscopy, including physician fees and facility overhead, was estimated to be $281.56 (see Table 1). After accounting for the number of first-degree family members, the age distribution of first-degree family members, the age-dependent clinical screening profiles, and discounting of future costs at a rate of 5% per year, the expected cost of the clinical screening strategy is estimated to be $9,607. This is the expected screening cost over time for all 6 first-degree family members of the FAP patient up to the point (if at all) where the family member expresses polyps and therefore discontinues screening.

Genetic testing and screening

Based on current reimbursement rates for genetic testing and professional interpretation, the cost of genetic testing in the proband is $1,297.71 (see Table 1). The more restrictive and focused test in first-degree family members is about a third of the cost at $457.30 per test. After accounting for the sensitivity of the genetic test in the proband, the number of first-degree family members, the age distribution of first-degree family members, the age-dependent clinical screening profiles for relative positive and relatives of proband negative cases, and discounting of future costs at a rate of 5% per year, the expected cost of the genetic testing and screening strategy is estimated to be $8,238. As with conventional clinical screening, this is the expected cost for all first-degree family members of the FAP patient. However, this expected cost also

includes genetic testing costs for the proband and first-degree family members who are tested (i.e. proband positive cases).

Incremental costs and uncertainty

In the base case analysis, the cost savings from reduced screening in some family members under the genetic test and screen strategy more than offset the additional cost of the genetic tests themselves by $1,369 ($9,607-$8,238). This means that for each new FAP family, the Ontario Ministry of Health can expect to save $1,369, on average, by adopting a policy of genetic testing as opposed to conventional screening for FAP families.

The results of varying values for 5 key model parameters are presented in Figures 2 through 6. In the base case the cost of the genetic test in the proband was $1,297.71. As shown in Figure 2, the genetic test and screen strategy remains less costly than conventional clinical screening as long as the cost of the genetic test is less than $2,666. It should be noted that this threshold value is twice the current reimbursement rate for the test and is, therefore, likely to be well beyond reasonable values for the cost of the test. A similar conclusion applies to the cost of the genetic test in family members (Figure 3). In the base case, the cost of the genetic test in family members is $457.30, and it is not until the cost of the test reaches $766 that the genetic test and screen strategy becomes more expensive than conventional clinical screening. However, as shown in Figure 4 the relative cost results are fairly sensitive to reasonable cost estimates for clinical screening. If the cost of clinical screening drops below $200 (from $281.56 in the base case), then conventional clinical screening becomes less costly than the genetic test and screen strategy.

Presented in Figure 5 is the sensitivity analysis on the sensitivity of genetic testing. Since the threshold value for the sensitivity of the genetic test of 0.36 is well below the accepted level from clinical trials, this variable does not impact substantially on the relative cost results. And finally, as shown in Figure 6, the number of first-degree FAP family members does appear to have an impact on the relative cost results. In the base case we assumed there would be 6 family members. However, if the number of family members is less than 4 (3.8 more specifically), than

the expected cost of the genetic test and screen strategy becomes more costly than conventional clinical screening.

DISCUSSION

We constructed a decision analytic model to compare the cost of conventional clinical screening to a strategy of genetic testing and screening in families of FAP patients. In the base case we found that genetic testing and screening was less costly compared to conventional screening by $1,369 per FAP family. A number of assumptions were required for this model and, therefore, the results should be interpreted with caution. Although the results were robust over reasonable values for most model parameters, the results were sensitive to the cost of clinical screening and the average number of FAP family members assumed in the model.

This model has several noteworthy limitations. First, this is an analysis of costs only and no relevant patient outcome measures, such as quality of life, have been included. Second, the analysis was conducted from the perspective of the Ontario Ministry of Health. A more comprehensive analysis would include costs to patients and other sectors of the economy. And third, the current model stops tracking costs once the patient develops polyps. A more complete cost analysis would include treatment for polyps (e.g. laser removal, surgery to remove colon) and the long-term costs and consequences of these treatment alternatives.

Table 1: Probability and cost estimates used in the decision analytic model of genetic testing in FAP

Variable	Baseline Estimate	Source
Sensitivity of genetic testing in proband	0.74	1
Risk of family member carrying ACP mutation	0.50	2,4
Probability of expressing ACP mutation	0.90	3
Detection of FAP polyps by age 20	0.90	1
Detection of FAP polyps by age 30	0.99	1
Detection of FAP polyps by age 40	1.00	1
Number of immediate relatives in family	6	7
Proportion of relatives aged 10-20 years	0.60	7
Proportion of relatives aged 20-30 years	0.20	7
Proportion of relatives aged 30-40 years	0.20	7
Cost of screening	$281.56	1,6
Cost of genetic test in proband	$1,297.71	5,6
Cost of genetic test in relative	$457.30	5,6

Sources:

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2. Bulow S, Burn J, Neale K, et al. The establishment of a polyposis register. Int J Colorectal Dis 1993; 8:34-38.

3. Prosser J, Condie A, Wright M, et al. ACP mutation analysis by chemical cleavage of mismatch and a protein truncation assay in familial adenomatous polyposis. Br J Cancer 1994; 61:841-846.

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5. Ontario Ministry of Health Diagnostic Testing Program.

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Figure 1: Decision analytic model used to compare costs of a genetic testing versus clinical screening strategy

Figure 2: Sensitivity analysis on cost of genetic testing in the proband

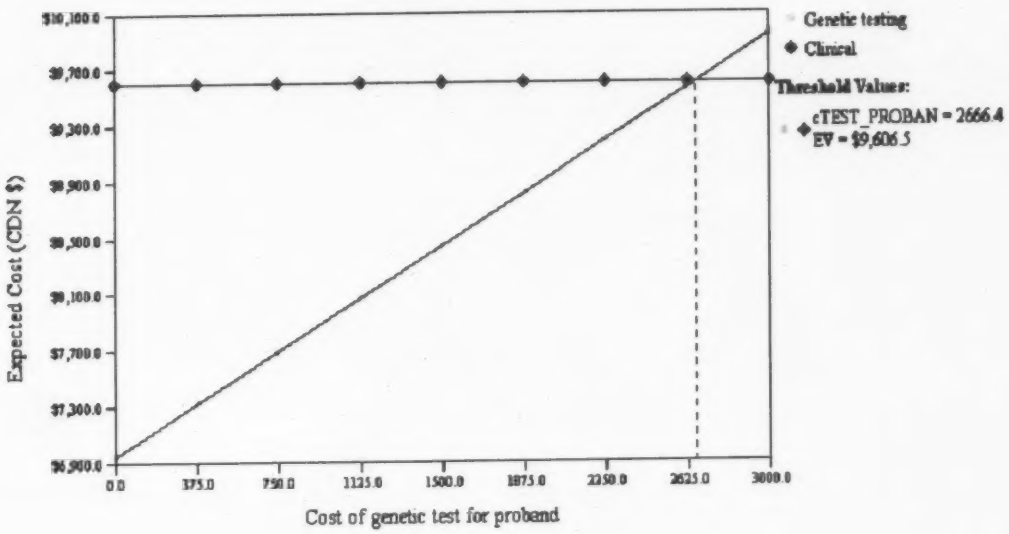


Figure 3: Sensitivity analysis on cost of genetic testing for first-degree family members

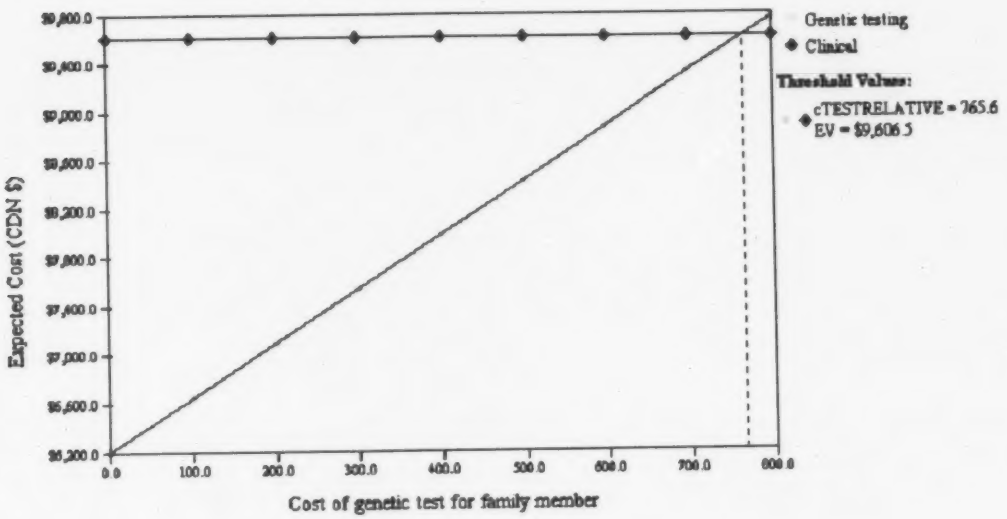


Figure 4: Sensitivity analysis on cost of clinical screening

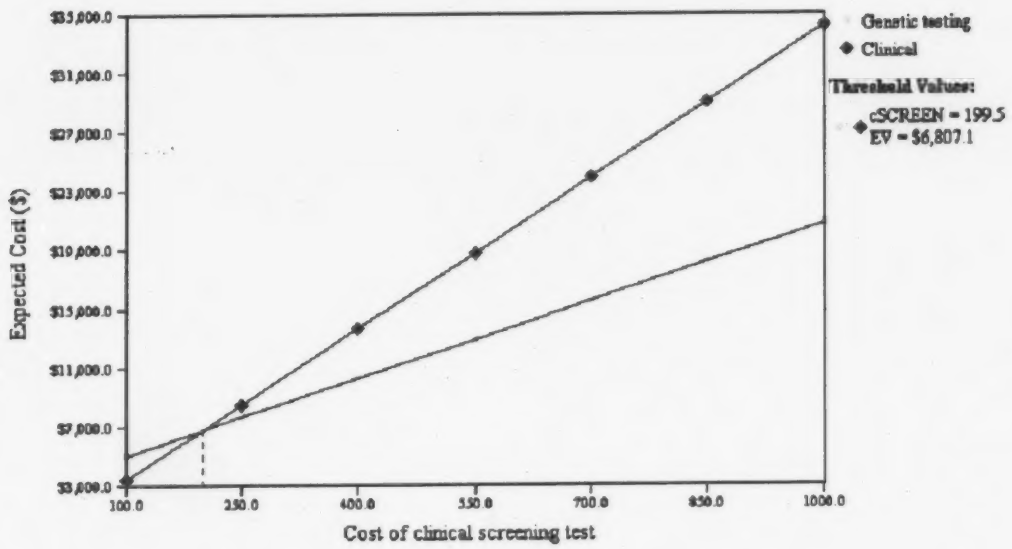


Figure 5: Sensitivity analysis on the sensitivity of genetic testing

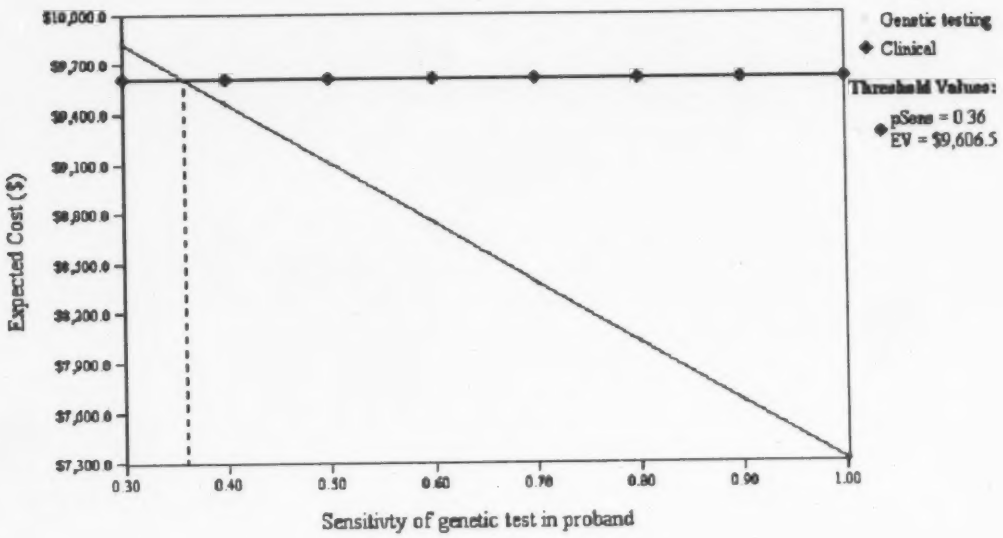
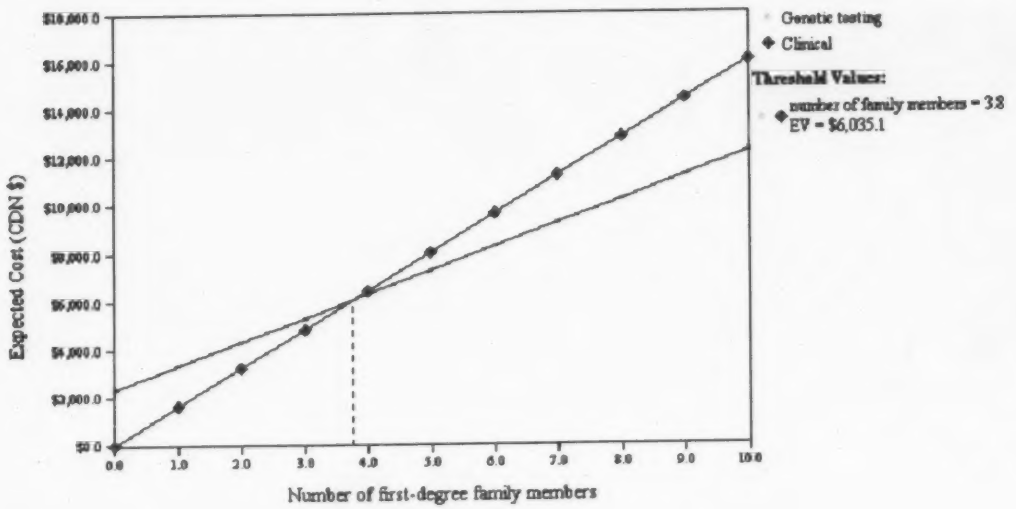


Figure 6: Sensitivity analysis on the number of first-degree family members



Appendix C: Costing model for APOE testing for Alzhiemer's Disease in Patients with Mild Cognitive Impairment

1. Introduction

Patients with Mild Cognitive Impairment (MCI) have a memory impairment beyond that expected for their age. A particular concern for patients with MCI is the risk of developing more severe impairments such as Alzheimer's Disease (AD). AD is a progressive neurodegenerative disorder with clinical symptoms of impairment in memory and language in early stages, progressing to loss of autonomy for self-care and need for full-time supervision in later stages. Between 6 and 8% of persons over the age of 65 have AD with the prevalence increasing to around 30% for persons over 85 years of age. Despite this high prevalence and significant impact on patient autonomy and quality of life, no cure exists for AD. Recently developed drugs such as Donepezil hydrochloride (Aricept) have been shown to be effective in delaying the onset of AD and in delaying disease progression in patients with confirmed AD. Early detection of gene mutations for AD allows patients to initiate preventative treatment to delay the onset of AD. However, since early detection only results in delayed disease onset, it is important to examine the up-front risks, benefits and cost of genotyping for AD.

2. Methods

A Markov model was developed to compare the cost of 2 general strategies for testing and treating patients with MCI who are at risk of developing AD. The starting point for the model is a patient with clinically diagnosed MCI. The first strategy (usual care) may include treatment for MCI (i.e. to delay AD onset) and/or treatment for AD (i.e. to slow disease progression) depending on patient and physician preference for treatment. The second strategy includes similar treatment with the addition of an up-front test to detect AD gene mutations. Therefore, the model essentially compares the up-front cost of genetic testing against the 'down stream' cost savings from delayed AD disease onset and lower AD prevention treatment costs. The cost

analysis was conducted from the perspective of the Ontario Ministry of Health and all costs are expressed in CA 2001 dollars.

2.1 Conventional treatment for MCI

The conventional treatment arm for MCI consists of 2 main components. The first component is the cost of treatment to delay AD onset and the second component is the cost of AD for progressive cases. Since patients with MCI may not go on to develop AD, not all MCI patients will agree to take AD preventative treatment. To a large extent this probability will be dictated by physician and patient preference. In the base case analysis we assume that one-fifth (20%) of MCI patients would take a drug to delay progression to AD and then vary this probability in a sensitivity analysis.

The second component of conventional treatment for MCI is the cost of AD for progressive cases. Previous studies show that approximately 50% of MCI patients develop AD after 4 years[1]. As with AD prevention treatment, not all confirmed AD patients will agree to treatment for AD. In the base case analysis we assume that one-half (50%) of AD patients will agree to AD treatment and then vary this probability in a sensitivity analysis. In this model the cost of AD is separated into the cost for patients on active AD treatment (e.g. Donepezil) and the cost of AD for patients not on active AD treatment. In addition to drug treatment costs, AD patients use the services of health care professionals, caregivers, community programs and long term care facilities. The cost of AD for patients on and not on active AD treatment was estimated and updated from a previously published economic analysis comparing Donepezil to usual care for AD in Canada[2].

2.2 Genetic testing for ApoE and treatment for MCI

The genetic testing and treatment arm consists of three components. The first two components are similar to conventional treatment. However, with genetic testing we assume in the base case that all patients (100%) with a positive genetic test and no patients (0%) with a negative test result will agree to take AD prevention treatment. In addition, we assume that one-half (50%) of MCI patients with a positive test result and one-fifth (20%) of patients with a negative genetic test result will go on to develop AD. The impact of these assumed probabilities on the cost analysis is tested through a series of sensitivity analyses.

The third component of the genetic testing and treatment arm is the cost of the genetic test itself and the probability the test will identify a mutation in an MCI population. In the base case we assume the genetic test costs $500 and that 40% of MCI patients will have a positive test result. The impact of alternative test costs and alternative probabilities of positive test results are examined through sensitivity analyses.

2.3 Markov model

We constructed a Markov model to compare the cost of conventional treatment for MCI compared to genetic testing and treatment. The model consists of two integrated components. The 'up-front' cost and outcome of the genetic test and the costs and outcomes of AD prevention treatment are modeled using a traditional decision tree structure (see Figure 1). The circles in the tree represent chance events that have associated probabilities of occurring. The genetic screening strategy is shown in the top portion of Figure 1. The test result can be positive or negative and based on this test result the patient may decide to take AD preventative treatment. Depending on a positive or negative test result the patient has an associated probability of developing AD. The conventional treatment strategy for MCI is shown in the bottom half of Figure 1. Once again, the patient may decide to take AD prevention treatment or not and has an associated probability of developing AD.

The additional 'down stream' costs and outcomes associated with patients who develop AD are added on to this decision tree structure using a Markov model from a previously published study on AD[2] (see Figure 2). Patients with AD may decide to take AD treatment or not as dictated by personal preference. In the base case we assume that one-half (50%) of AD patients will take active treatment for their AD. The AD Markov model sub-tree has six health states, five representing different levels of cognition (as measured using the Mini Mental State Exam – MMSE) and one competing death state. We assume that patients entering the Markov model sub-tree from MCI enter the mild AD health state (i.e. MMSE 21-26). Information on how patients progress through the AD health states over time, whether on active treatment or not, was derived from Donepezil clinical trial data and is described in more detail in the original economic manuscript[2].

The baseline probability and cost estimates used in the model are presented in Table 1. Shown in Table 1 are the base case values for the probability of finding a mutated gene in the MCI patient, the probability of seeking AD prevention treatment, the probability of developing AD, the progression time from MCI to AD, the cost of the genetic test and the cost of AD treatment. In the base case the temporal model perspective is 8 years and the discount rate used for future costs is set at 3%.

2.4 Sensitivity analysis

The expected cost of each strategy can be determined by using base case or 'best estimates' for each model parameter. However, since the values for most model parameters are not known with certainty, it is common to test the impact of alternative values for these parameters. This is known as sensitivity analysis. For the present study, we conducted sensitivity analyses on the following key model parameters: cost of the genetic test; probability of finding a gene mutation in MCI patients; delay in progression from MCI to AD with AD prevention treatment; probability of seeking AD prevention treatment; probability of developing AD; and probability of seeking AD treatment.

3. Results

3.1 Conventional treatment for MCI

After accounting for the probability of seeking AD prevention treatment, the proportion of patients that go on to develop AD, the probability of seeking treatment for AD, and the cost of AD treatment, the expected 8 year cost of conventional treatment for MCI patients is estimated to be $24,245 per patient.

3.2 Genetic testing for ApoE and treatment for MCI

When the cost of genetic testing is included and assuming that 40% of MCI patients have a mutated gene, the 8 year cost of the genetic test and treat strategy is expected to be $24,824 per patient.

3.3 Incremental costs and uncertainty

In the base case analysis, the cost savings from reduced AD prevention costs in the genetic test and treat strategy for patients who test negative for the mutated gene are not enough to offset the

additional cost of the genetic test. This means that for each new MCI patient the Ontario Ministry of Health can expect to spend an extra $579, on average, per patient by adopting a policy of genetic testing as opposed to conventional treatment.

These are the base case or 'best guess' results. However, there are a number of assumptions that went into the model. Not reported here are the results of alternative assumptions for model parameters that did not have a large impact on the relative cost results. The relative cost results were fairly insensitive to alternative assumptions for the following model parameters: the mean number of months before MCI progresses to AD for untreated patients; the probability of developing AD in patients with a negative mutation test result; the probability of seeking treatment for AD; and the cost of AD (with or without active AD treatment). The results of varying values for 7 other key model parameters demonstrate that the relative cost findings (i.e. that the genetic test and treat strategy is cost increasing) are sensitive to a number of important model variables. These results are presented in Figures 3 through 9 and discussed in turn below.

In the base case the cost of the genetic test was assumed to be $500. As shown in Figure 3, the expected cost in the genetic test and treat strategy is very sensitive to the cost of the genetic test. Since it is assumed that all patients in the genetic test and treat strategy receive a genetic test, the cost of the test adds one-to-one to the incremental cost difference between the two strategies. However, even if the cost of the genetic test is only $200, the genetic test and treat strategy remains more costly than conventional MCI treatment.

Based on findings reported in the literature, it was assumed that approximately 40% of MCI patients would have a mutated gene in the base case. The results in Figure 4 show that if this probability decreases below 26%, then the genetic test and treat strategy becomes slightly less expensive. Since the threshold value is close to the base case value used in the model, the proportion of MCI patients who are likely to have a mutated gene is an important variable determining which strategy is least costly.

The relative cost results were fairly insensitive to the mean number of months it takes MCI, on

average, to progress to AD. However, the relative cost results were sensitive to the assumed delay to AD progression with AD prevention treatment. In the base case we assumed that it would take 30 months, on average, for MCI to progress to AD and that AD prevention treatment would delay this progression by an average of 6 months. The results in Figure 5 suggest that if the delay to AD with AD prevention treatment is more than 9 months, then the genetic test and treat strategy becomes less costly than conventional MCI treatment. Although preliminary clinical trial results suggest this delay is about 6 months, the actual delay period may be longer. If this turns out to be the case then the genetic test and treat strategy may be cost reducing overall.

The results in Figure 6 show that the genetic test and treat strategy becomes less costly than conventional MCI treatment when the probability of seeking AD prevention treatment, with the knowledge of a positive genetic test, falls below 56%. In the base case, we assumed that 100% of patients with a positive test result would seek AD prevention treatment. However, the probability of seeking treatment will be driven by physician and patient perceptions of patient risk and the perceived efficacy of AD prevention treatment. Once clinical trials are complete and the drugs are available for the prevention indication, then drug surveillance studies of physician prescribing patterns and patient compliance can be used to better estimate this probability.

In the base case we assumed that 0% of patients would seek AD prevention treatment if the genetic test was negative. As shown in Figure 7, the expected cost in the genetic test and treat strategy was very sensitive to this probability. However, the genetic test and treat strategy remained more costly throughout the ranges considered.

The relative cost results are sensitive to the value assumed for the probability of seeking AD prevention treatment given the patient did not have a genetic test (i.e. conventional treatment arm). In the base case we assumed that 20% of MCI patients would seek AD prevention treatment. As shown in Figure 8, if the proportion rises above 30% then the genetic test and treat strategy becomes less costly than conventional MCI treatment. Since this threshold value is close to the base case probability used in the model, drug surveillance studies of physician prescribing and patient compliance will be important inputs into the model.

And finally, the relative cost results are sensitive to the value assumed for the probability of developing AD given the patient had a positive genetic test result. In the base case we assumed that 50% of MCI patients with a positive genetic test result would go on to develop AD. This proportion is consistent with findings from the literature[1]. As shown in Figure 9, if the proportion rises above 61% then the genetic test and treat strategy becomes less costly than conventional MCI treatment. This threshold value is also close to the base case probability used in the model. Therefore, a more comprehensive and systematic review of long term follow-up studies of MCI patients is needed to better inform this probability.

4 Discussion

We constructed a decision analytic model to compare the cost of conventional treatment for MCI patients to a strategy of genetic testing and treatment. In the base case we found that the genetic test and treat strategy was more costly compared to conventional treatment by $579 per MCI patient on average. However, a number of assumptions were required for this model. Although the results were robust over reasonable values for some of the model parameters, the relative cost results were very sensitive to 7 key model variables, 5 of which showed threshold values close to, or within a reasonable range of, the base case values. As a result, until more firm values are available for these key model variables, the relative cost results should be interpreted with caution.

This model has two noteworthy limitations. First, this is an analysis of costs only and no relevant patient outcome measures, such as quality of life, have been included. Second, the analysis was conducted from the perspective of the Ontario Ministry of Health. A more comprehensive analysis would include costs to patients and other sectors of the economy.

5. References (Appendix C)

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Table 1: Probability and cost estimates used in the decision analytic model of genetic testing in MCI

Variable	Baseline Estimate
Probability of finding a gene mutation in MCI patient	0.40
Probability of seeking AD prevention treatment given:	
Positive genetic test result	1.0
Negative genetic test result	0
No genetic test	0.2
Probability of developing AD given:	
Positive genetic test result	0.5
Negative genetic test result	0.2
No genetic test	0.32
Mean time (in months) from MCI to AD given:	
No AD prevention treatment	30
AD prevention treatment (6 month delay over no treatment)	24
Probability of taking AD treatment	0.5
Cost of genetic test	$500
Cost of treatment for:	
AD prevention (delay)	$5.11[1]
AD treatment	$5.11[1]

[1] – includes pharmacy mark-up

Figure 1: **Decision analytic model used to compare costs of a genetic testing and treatment versus conventional treatment for MCI patients**

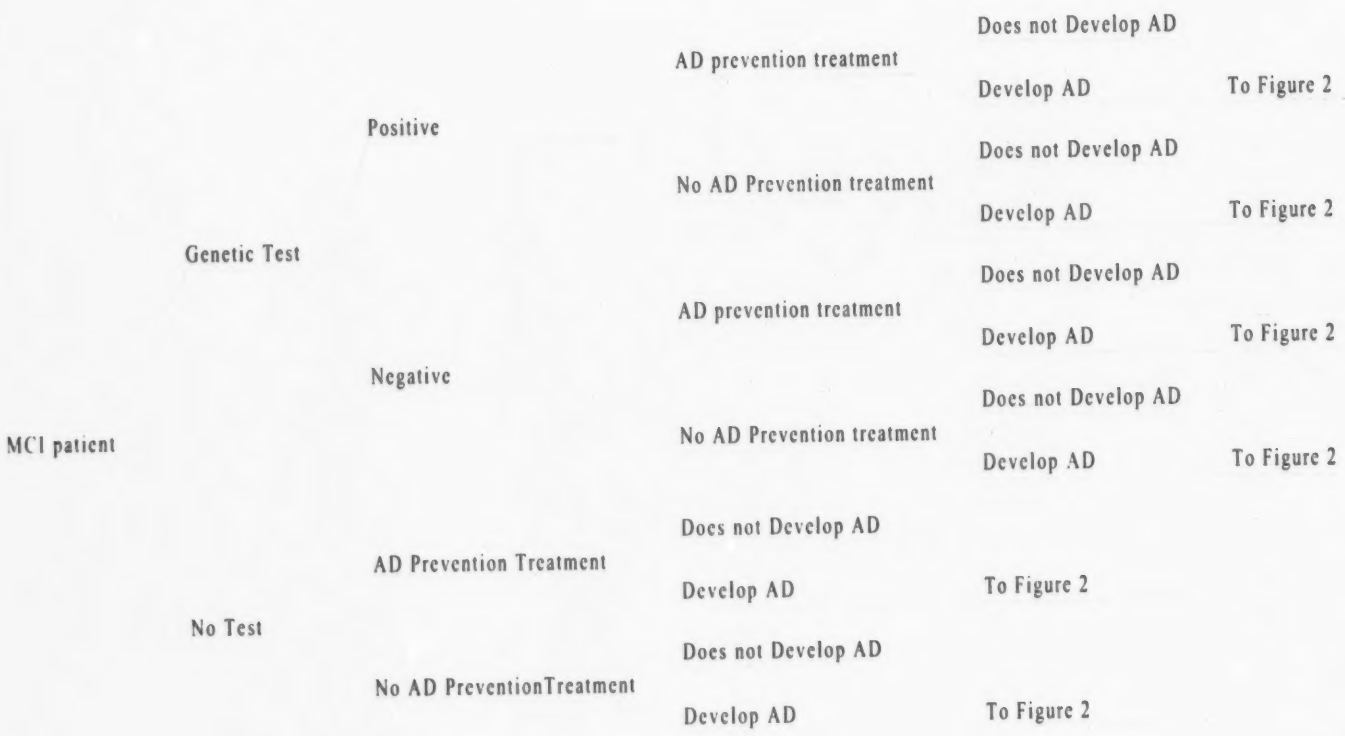


Figure 2: **Markov Model sub-tree used to cost AD with and without active treatment**

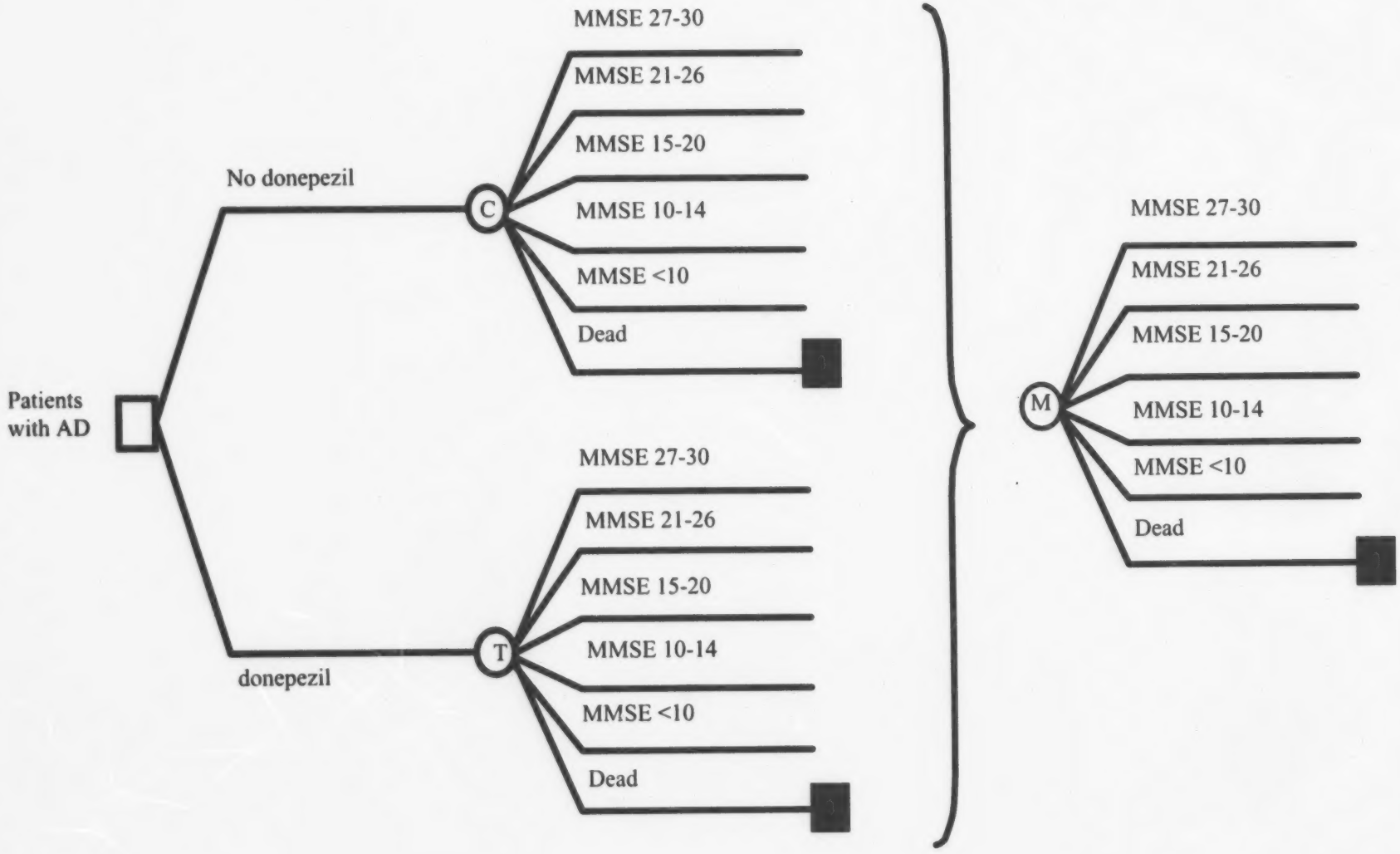


Figure 3: Sensitivity analysis on cost of genetic testing

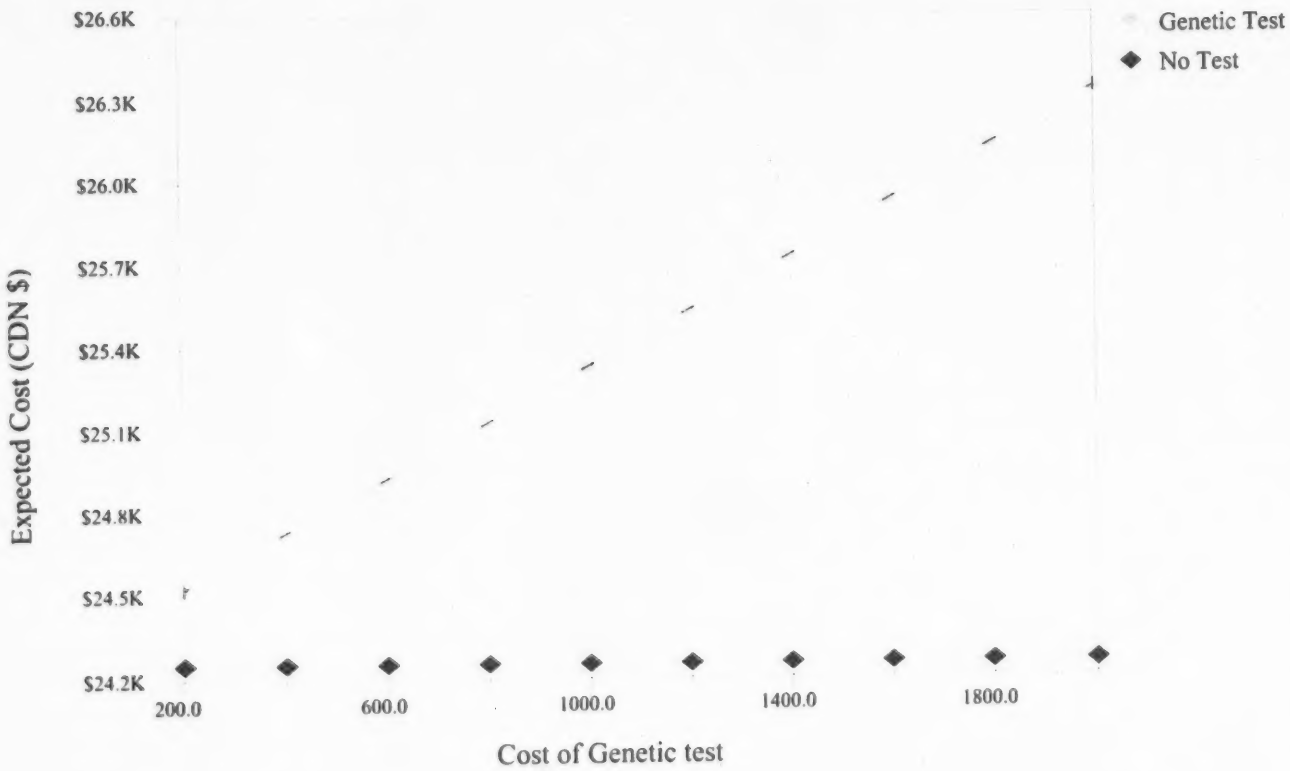


Figure 4: **Sensitivity analysis on probability of finding a gene mutation**

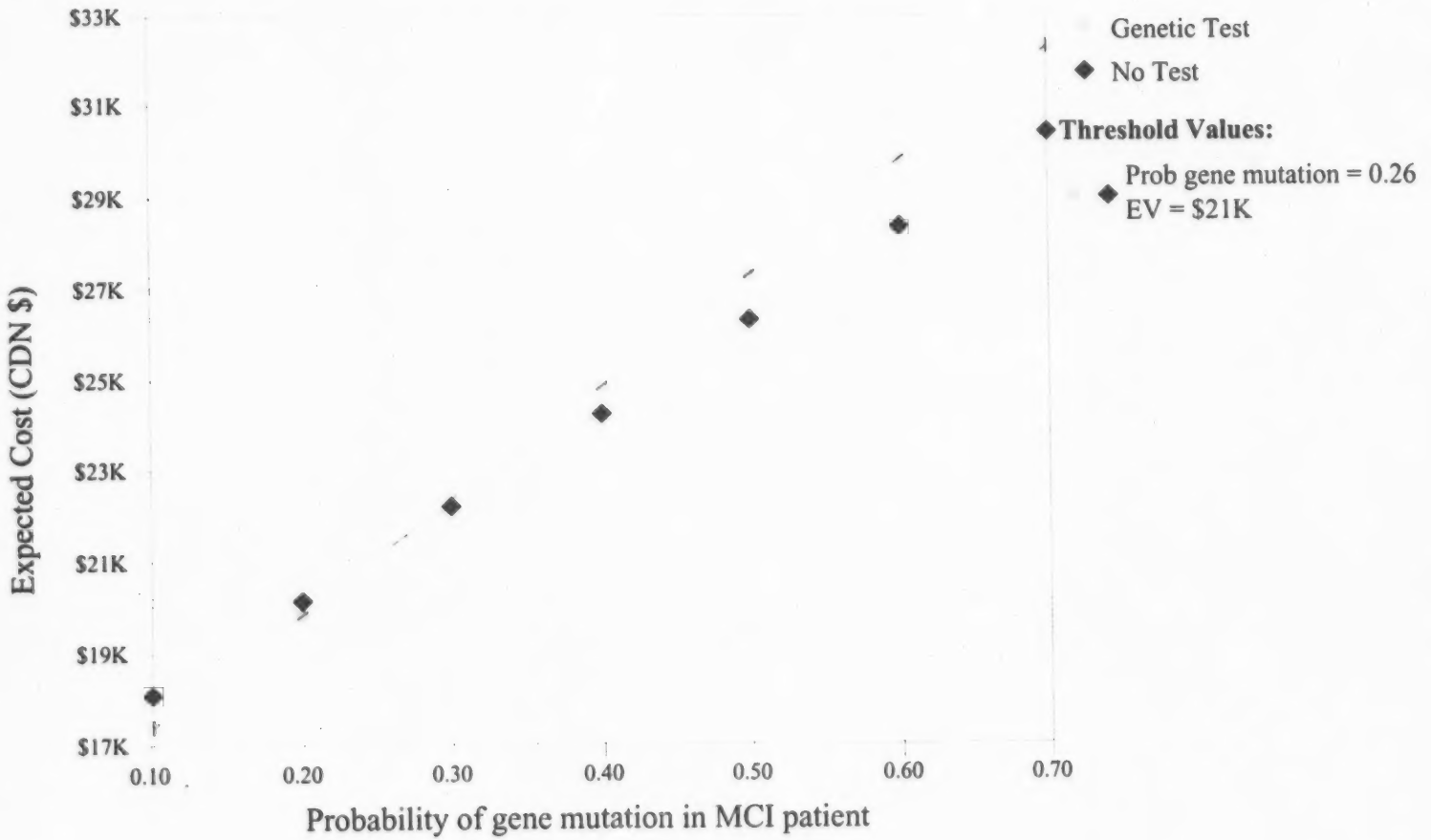


Figure 5: **Sensitivity analysis on delay to AD progression with AD prevention treatment**

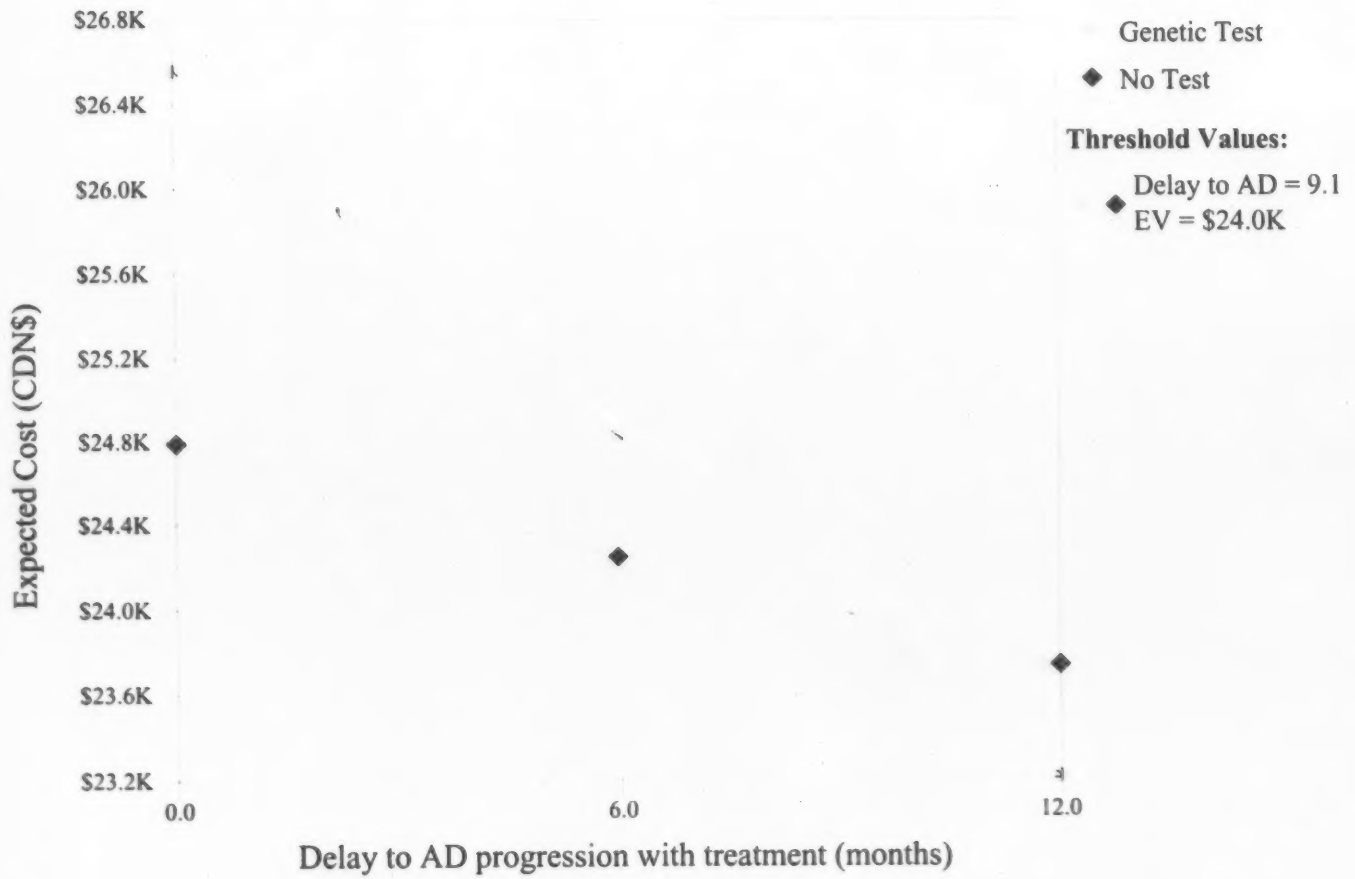


Figure 6: **Sensitivity analysis on seeking AD prevention treatment if positive test result**

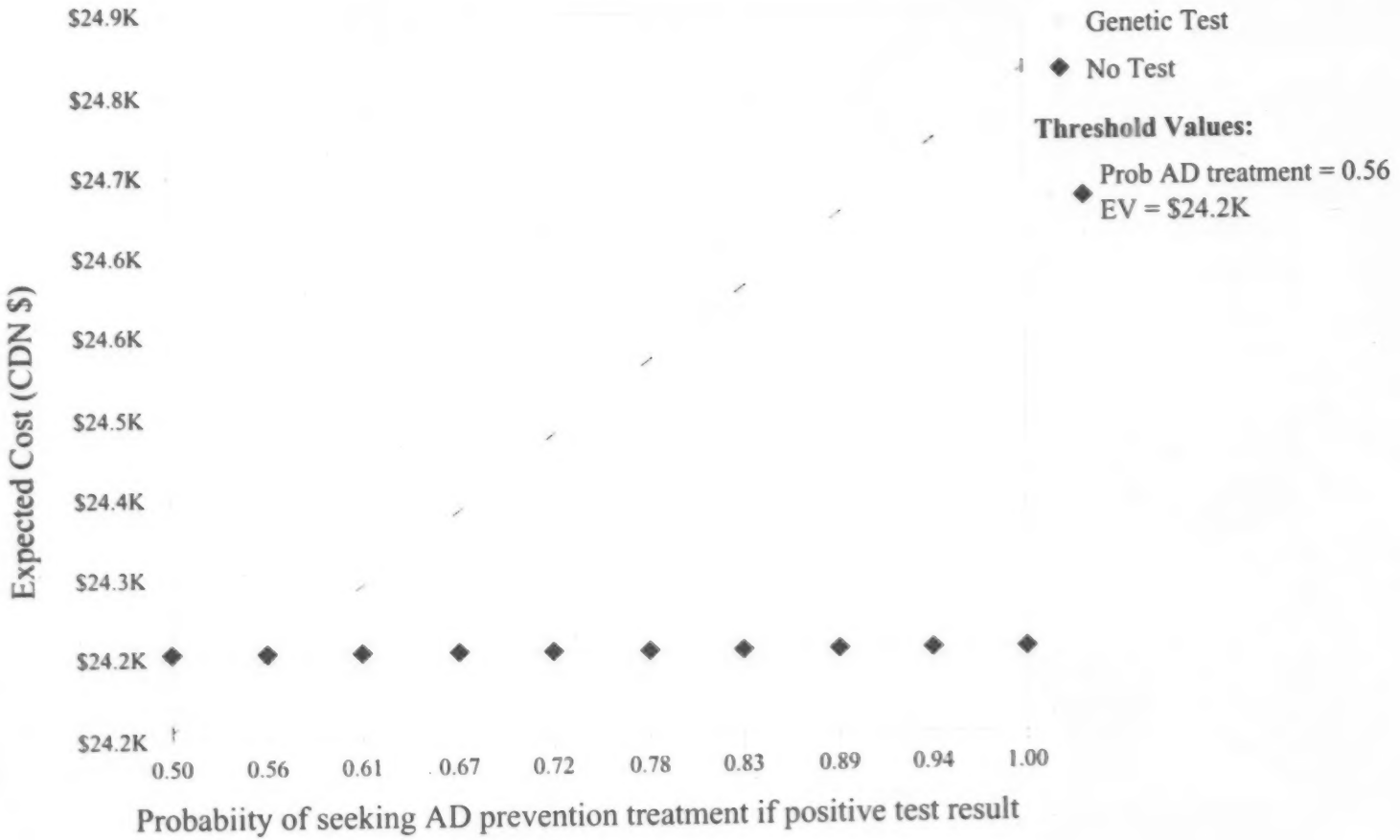

$24.9K
$24.8K
$24.7K
$24.6K
$24.6K
$24.5K
$24.4K
$24.3K
$24.2K
$24.2K
Expected Cost (CDN $)
0.50
0.56
0.61
0.67
0.72
0.78
0.83
0.89
0.94
1.00
Probabiity of seeking AD prevention treatment if positive test result
Genetic Test
No Test
Threshold Values:
Prob AD treatment = 0.56
EV = $24.2K

Figure 7: Sensitivity analysis on seeking AD prevention treatment if negative test result

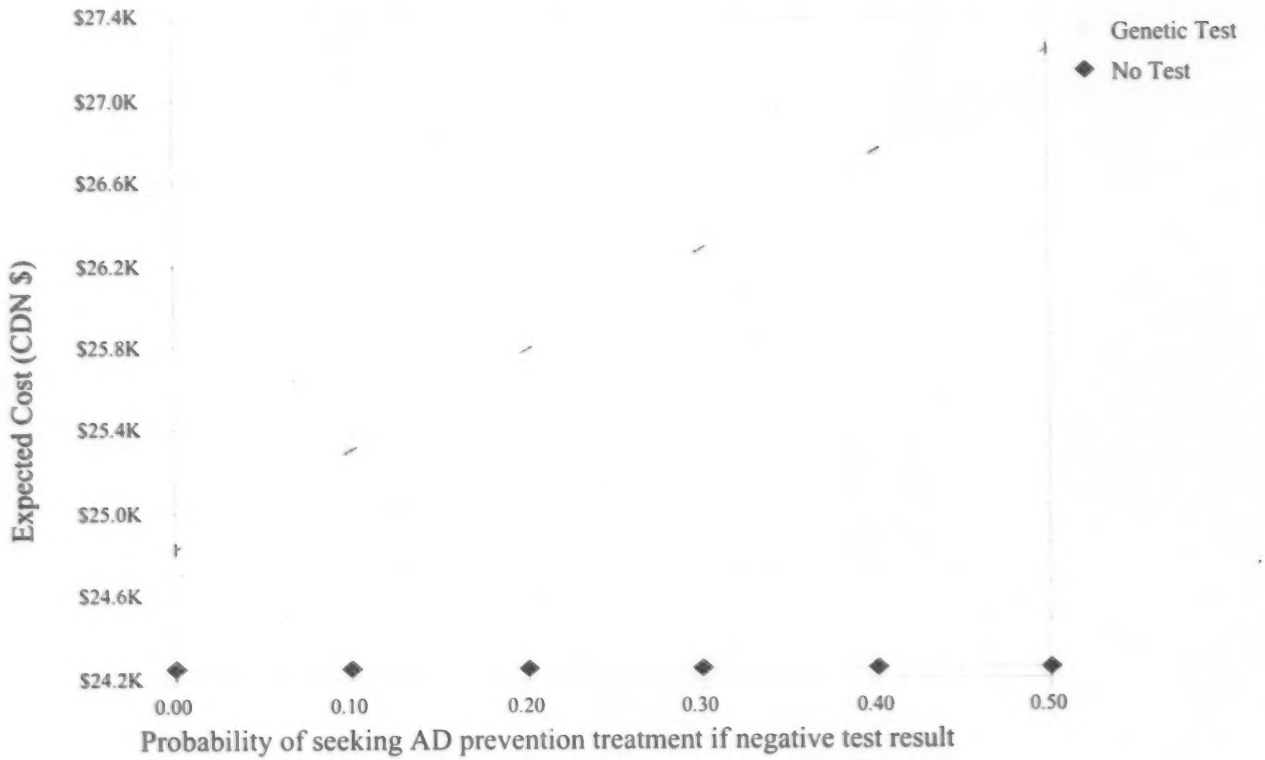


Figure 8: **Sensitivity analysis on seeking AD prevention treatment if no genetic test**

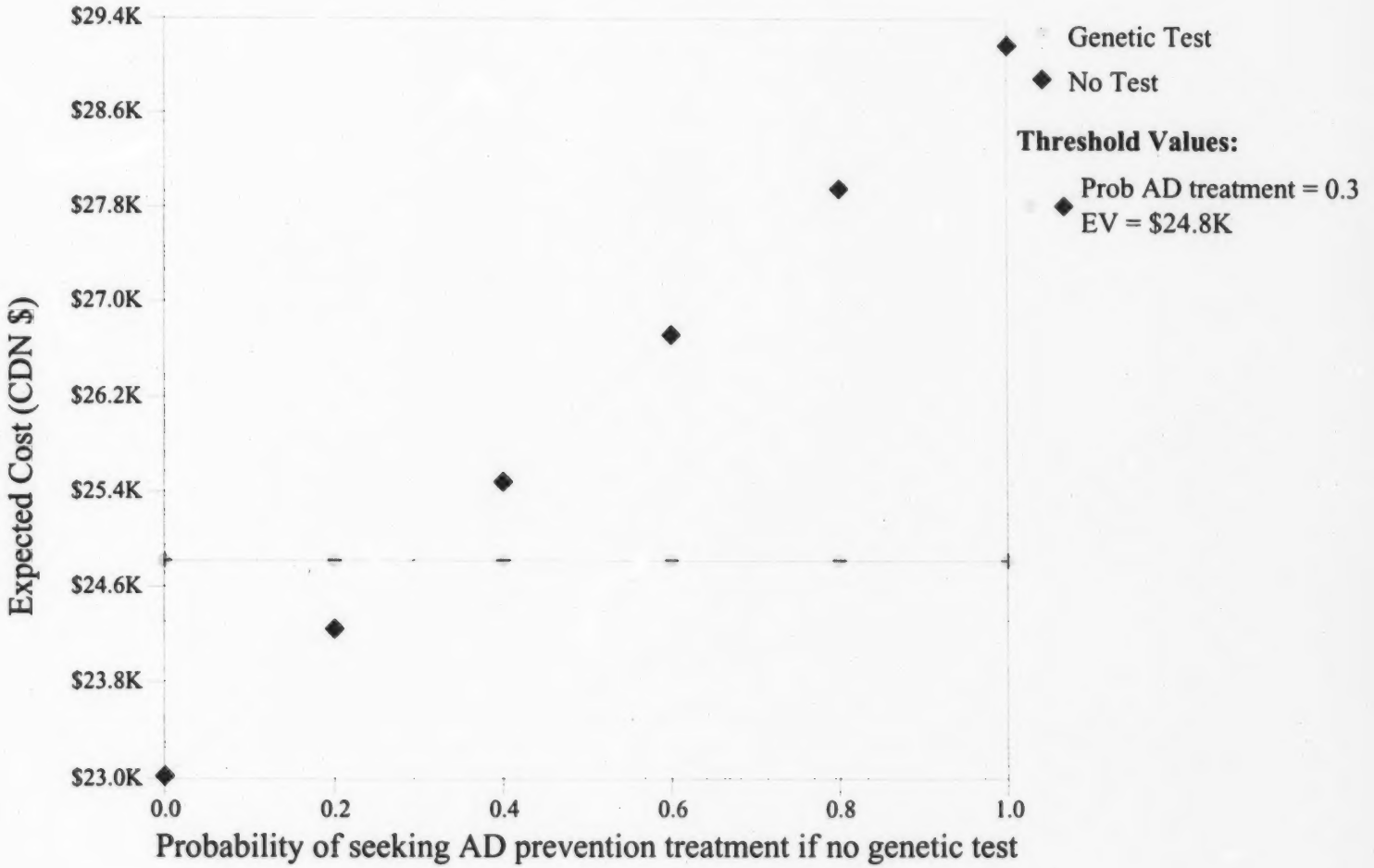
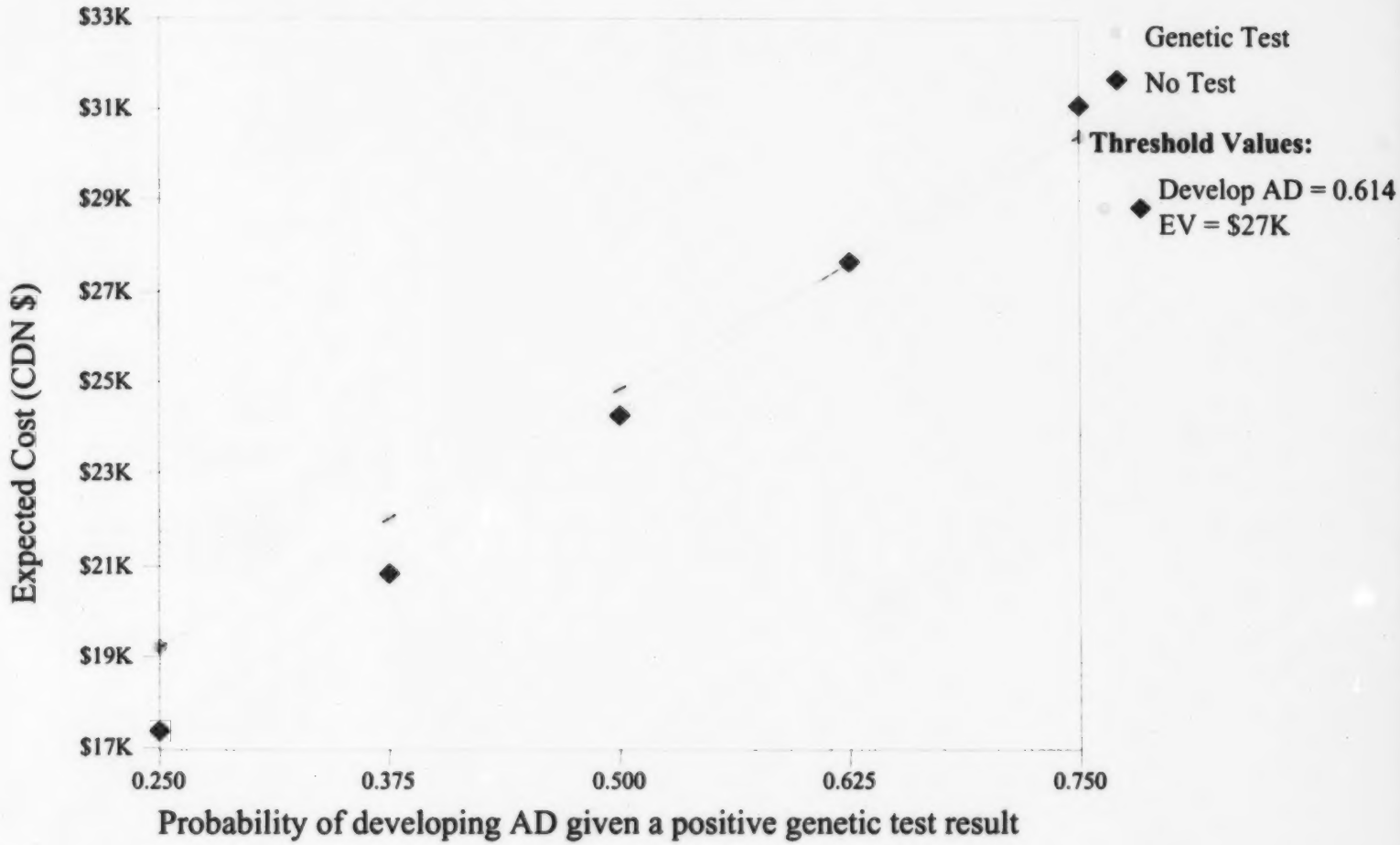

$29.4K
$28.6K
$27.8K
$27.0K
$26.2K
$25.4K
$24.6K
$23.8K
$23.0K
Expected Cost (CDN $)
0.0
0.2
0.4
0.6
0.8
1.0
Probability of seeking AD prevention treatment if no genetic test
Genetic Test
No Test
Threshold Values:
Prob AD treatment = 0.3
EV = $24.8K

Figure 9: **Sensitivity analysis on probability of developing AD if a positive genetic test result**


$33K
$31K
$29K
$27K
$25K
$23K
$21K
$19K
$17K
Expected Cost (CDN $)
0.250
0.375
0.500
0.625
0.750
Probability of developing AD given a positive genetic test result
Genetic Test
No Test
Threshold Values:
Develop AD = 0.614
EV = $27K

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